Exercise Physiology for the Pediatric and Congenital Cardiologist

Jonathan Rhodes
Mark E. Alexander
Alexander R. Opotowsky
Editors

Springer

Exercise Physiology for the Pediatric and Congenital Cardiologist

Jonathan Rhodes
Mark E. Alexander
Alexander R. Opotowsky
Editors

Exercise Physiology for the Pediatric and Congenital Cardiologist

Springer

Editors
Jonathan Rhodes, MD
Department of Pediatrics
Harvard Medical School
Boston, MA
USA

Mark E. Alexander, MD
Department of Pediatrics
Harvard Medical School
Boston, MA
USA

Alexander R. Opotowsky, MD, MPH
Department of Pediatrics
Harvard Medical School
Boston, MA
USA

ISBN 978-3-030-16817-9 ISBN 978-3-030-16818-6 (eBook)
https://doi.org/10.1007/978-3-030-16818-6

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To Janet, who has loved and supported me through everything, raised five wonderful children, and added spirituality to my life. How long have we been married??? Not long enough!

Jonathan Rhodes

To Lori, over 34 years of OB call, child rearing, sage advice and amusement at the many ways academic medicine can keep her husband busy, tolerated this and all the tasks that have let our careers and marriage thrive. Thank you again.

Mark E. Alexander

To my parents, Barbara and Stuart, who poured for me a foundation of curiosity, love of spirited debate, and zest for understanding.

Alexander R. Opotowsky

Preface

Rhodes' Postulates and the Reasons Why Pediatric and Congenital Cardiologists Should Study Exercise Physiology

1. 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.
2. This function is maximally stressed when an individual's metabolic rate is increased, a condition that occurs most commonly during physical activity/exercise.
3. Consequently, cardiopulmonary exercise testing (CPET) can provide clinicians with a wealth of data concerning the capabilities and health of the cardiovascular system.

These three premises (known colloquially, within the corridors of Boston Children's Hospital, as "Rhodes' Postulates") underlie the science and practice of exercise physiology testing in patients with congenital heart disease (CHD) and other pediatric cardiovascular disorders.

Since the widespread application of modern CPET technology to patients with CHD (a process that did not really begin until the 1990s), innumerable clinical studies have confirmed the validity of these premises. These studies have generated many intriguing and clinically useful insights into the effect of CHD upon a patient's ability to exercise.

Data from CPET have been found to provide reproducible, objective, and quantitative assessments of a patient's clinical status. Moreover, in many cases, CPET data can provide clinicians with valuable, *noninvasive* prognostic information, help identify targets for therapeutic intervention, and permit objective, quantitative assessments of therapeutic interventions.

Indeed, in many institutions, CPET has become an integral component of the evaluation and management of patients with CHD. For this reason alone, it is important for practitioners who care for patients with CHD and other pediatric cardiovascular disorders to be familiar with the concepts of exercise physiology and the capabilities of CPET.

Of perhaps even greater importance, however, is the exceptional understanding of physiology that can be acquired when one studies the effects that the diverse, unique lesions encountered in the world of pediatric cardiology

may have upon the cardiopulmonary adaptations to exercise. This understanding can be productively applied to other clinical settings including the cardiac intensive care unit, the operating room, the catheterization laboratory, the imaging laboratories, and the outpatient cardiology clinic.

Consequently, there is a need for a textbook that can help teach and explain the concepts of exercise physiology as they pertain to CHD and provide a comprehensive roadmap for this fascinating and often complex discipline. It is my hope that this undertaking will serve this purpose.

Clinical Value of Cardiopulmonary Exercise Testing in Patients with CHD and Other Disorders

What causes a patient to stop exercising? Is it her heart? Is it his lungs? Is it a lack of motivation? Is there a metabolic, neuromuscular, hematologic, or other disorder? Can we be a bit more sophisticated about the cause of an individual's exercise limitation: If it is a cardiovascular issue, is it related to an inability to increase the heart rate normally in response to exercise, or is it related to an inability to augment the stroke volume (or both)? What might be impairing the stroke volume response to exercise? Is it a myocardial problem, a valvular problem, or a problem with the systemic, pulmonary, or coronary circulations? Might a shunt lesion be contributing to the pathophysiology? Is there an electrophysiologic issue? If the patient's exercise function is limited by pulmonary factors, can we determine whether obstructive lung disease, restrictive physiology, ventilation/perfusion mismatch, and/or abnormal gas transport across the alveolar- capillary membrane are operative?

Data from modern cardiopulmonary exercise testing (CPET) can shed light on these issues, as well as other important clinical questions such as the following: How does the patient's exercise capacity compare to normal subjects? How does it compare to other patients with similar diseases? How has the patient's exercise function and cardiopulmonary response to exercise changed over time? Can data from the exercise test help identify any targets for therapeutic intervention? Can we objectively assess the effectiveness of a clinical intervention? Does exercise pose a risk for this patient? Can anything be done to reduce the risk of exercise, and can the effectiveness of these risk-lowering strategies be assessed? Can data from CPET tell us anything about a patient's prognosis?

The myriad diagnoses and conditions encountered within the fields of pediatric and congenital cardiology present unique challenges to the cardiologist attempting to tease out answers to these (and other) questions from the wealth of data that may be acquired during modern exercise physiology testing. They also present unique opportunities to explore and better understand how the cardiopulmonary system adapts to the demands of exercise during health and disease. These undertakings must be based, however, upon a firm understanding of the normal cardiopulmonary response to exercise. This will be the focus of the first section of this textbook. We will then discuss the conduct and interpretation of the CPET. Thereafter, we will see how the principles of exercise physiology may be applied to patients with specific

congenital and pediatric cardiovascular disorders. Finally, some interesting cases that illustrate the fascinating physiology that may be encountered in the fields of pediatric and congenital cardiology will be presented and discussed.

Boston, MA, USA Jonathan Rhodes

Contents

Contributors

Dominic J. Abrams, MD, MRCP Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Inherited Cardiac Arrhythmia Program, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Mark E. Alexander, MD, FHRS Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Exercise Physiology, Arrhythmia Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Shankar Baskar, MD Arrhythmia Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Vassilios J. Bezzerides, MD, PhD Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Arrhythmia Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Laura Bourette, MS Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Arene Butto, MD Advanced Cardiac Therapies and Cardiac Intensive Care, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Stephanie F. Chandler, MD Department of Cardiology, Ann and Robert H. Lurie Children's Hospital, Chicago, IL, USA

Department of Pediatrics, Northwestern Feinberg School of Medicine, Chicago, IL, USA

Ming Hui Chen, MD, MMSc Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA

Tracy J. Curran, PhD Exercise Physiology, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Audrey Dionne, MD Arrhythmia Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Iqbal El-Assaad, MD Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Naomi S. Gauthier, MD Cardiac Fitness Program, Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Jennifer Huang, MD, MCr Exercise Physiology, Ambulatory and Outreach Services, Department of Pediatrics, Doernbecher Children's Hospital, Oregon Health and Science University, Portland, OR, USA

Robyn J. Hylind, MS, CGC Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Irene D. Lytrivi, MD Department of Pediatrics, Columbia University Medical College, New York, NY, USA

Program for Pediatric Cardiomyopathy, Heart Failure and Transplantation, Division of Pediatric Cardiology, Columbia Presbyterian Hospital, New York, NY, USA

Renee Margossian, MD Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Edward T. O'Leary, MD Arrhythmia Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Julieann O'Neill, MS Exercise Physiology, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Alexander R. Opotowsky, MD, MPH, MMSc Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Exercise Physiology Laboratory, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Tam Dan N. Pham, MD Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Jennifer L. Pymm, MS Exercise Physiology, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Jonathan Rhodes, MD Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Keri M. Shafer, MD Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

T. P. Singh, MD, MSc Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Heart Failure/Transplant Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Ana Ubeda-Tikkanen, MD, PhD Physical Medicine and Rehabilitation, Department of Pediatric Rehabilitation, Boston Children's Hospital, Boston, MA, USA

Physical Medicine and Rehabilitation, Department of Pediatric Rehabilitation, Spaulding Rehabilitation Hospital, Boston, MA, USA

Physical Medicine and Rehabilitation, Department of Pediatric Rehabilitation, Harvard Medical School, Boston, MA, USA

Part I

The Normal Cardiopulmonary Response to Exercise

Biochemistry of Exercise

1

Jonathan Rhodes

Before we embark upon a discussion of the normal cardiopulmonary response to exercise, it would be beneficial to review some of the basic biochemistry that relates to exercise. The energy required to perform the mechanical work of exercise is derived from the hydrolysis of adenosine triphosphate (ATP). At rest, skeletal muscle cells possess only limited quantities of ATP and other high-energy phosphate molecules. If exercise is to be continued for more than a brief period of time, ATP must be continually replenished through the metabolism of fuels—primarily fats and carbohydrates. The aerobic metabolism of each carbon atom within the side chain of a fatty acid may be expressed by the equation:

$$H-C-H+1\frac{1}{2}O_2 \rightarrow CO_2+H_2O+\sim 8\,ATP;\,RQ=0.67$$

This equation indicates that each carbon atom within the side chain reacts with one-and-a-half molecules of O_2 to form one molecule of CO_2, water, and about eight molecules of ATP. The respiratory quotient for this reaction (RQ, the ratio of the moles of CO_2 produced divided by the number of moles of O_2 consumed) is 0.67.

The aerobic metabolism of each carbon atom within a carbohydrate or sugar may be expressed by the equation:

$$H-C-OH+O_2 \rightarrow CO_2+H_2O+\sim 6\,ATP;\,RQ=1.0$$

This equation indicates that each carbon atom within the carbohydrate molecule reacts with one molecule of O_2 to form one molecule of CO_2, water, and about six molecules of ATP. The respiratory quotient for this reaction is 1.00. Hence, the aerobic metabolism of glucose, a six-carbon sugar, produces ~36 molecules of ATP.

In the absence of O_2, ATP may also be produced via anaerobic metabolism. The anaerobic metabolism of glucose is expressed by the equation:

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \rightarrow 2\underset{\text{Lactic acid}}{CH_3CHOHCOOH} + 2\,ATP\left(\sim 0.33\,ATP/C\right)$$

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_1

This equation indicates that ATP can be produced via anaerobic metabolism *without consuming* O_2, although the amount of ATP produced per carbon atom is much smaller than that which can be derived from aerobic metabolism. However, although anaerobic metabolism (glycolysis) extracts only a small fraction of the energy available from the glucose molecule, the kinetics of the glycolytic pathway are very rapid and a large amount of ATP can in fact be produced through this pathway, albeit for only a limited period of time (on account of the accumulation of lactic acid).

Lactic acid is actually produced by the reduction of pyruvic acid, formed in the last step of the glycolytic pathway, by $NADH_2$ present with the cell and/or produced earlier in the pathway:

$$\underset{\text{Pyruvic acid}}{CH_3COCOOH} + NADH_2^+ \rightarrow \underset{\text{Lactic acid}}{CH_3CHOHCOOH} + NAD^+$$

Hence, if oxygen is not available to oxidize $NADH_2$, the lactate/pyruvate ratio and the $NADH_2$/NAD ratio within the cell will rise.

Each molecule of lactic acid produced by the anaerobic metabolism of glucose may then be buffered by a bicarbonate ion to form a lactate ion, CO_2, and water:

$$\underset{\text{Lactic acid}}{CH_3CHOHCOOH} + \underset{\text{Bicarbonate}}{HCO_3^-} \rightarrow \underset{\text{Lactate}}{CH_3CHOHCOO^-} + H_2O + CO_2$$

Hence, when a muscle cell generates ATP from anaerobic metabolism, it does not consume O_2, but it does produce lactic acid and, indirectly, CO_2.

These equations help us to understand the two fundamental challenges that exercise poses to the cardiopulmonary system: (1) how to deliver sufficient quantities of O_2 to the exercising muscles, and (2) how to eliminate the increased quantities of CO_2 that are produced by the exercising muscles. The manner in which the cardiopulmonary system adapts to these two challenges and how, in general, congenital and other pediatric cardiovascular disorders may impair these adaptations will now be discussed.

Suggested Readings

1. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun X-G, et al. Principles of exercise testing and interpretation. 5th ed. Philadelphia: Lippincott; 2012. p. 1–4.
2. Jones NL. Clinical exercise testing. 4th ed. Philadelphia: W. B. Saunders; 1997. p. 14–23.
3. Nelson DL, Cox MM. Lehninger's principles of biochemistry. 7th ed. New York: W. H. Freeman & Co; 2017. p. 1441–2003.

Oxygen Delivery

2

Jonathan Rhodes

The mechanisms by which the cardiovascular system delivers oxygen to the skeletal muscles are best understood from consideration of Fick equation:

$$\begin{aligned}\dot{V}_{O2} &= [\text{C.O.}] \times [\text{oxygen extraction}] \\ &= [\text{HR} \times \text{SV}] \times [C_aO_2 - C_vO_2] \\ &= [\text{HR} \times \text{SV}] \times [1.36(\text{Hgb})(S_aO_2 - S_vO_2)]\end{aligned}$$

($\dot{V}_{O2,}$ oxygen consumption; CO, cardiac output; HR, heart rate; SV, stroke volume; C_aO_2, arterial oxygen content; C_vO_2, venous oxygen content; Hgb, hemoglobin concentration; S_aO_2, arterial oxygen saturation; S_vO_2, venous oxygen saturation. This equation ignores the small amount of dissolved oxygen, which in room air is negligible.)

Normally, during exercise, each of these variables is altered so as to maximize oxygen delivery.

Heart Rate

During exercise, heart rate rises up to threefold from the resting values of 60–80 bpm to ~200 bpm at peak exercise. This rise is mediated primarily by the autonomic nervous system via an increase in sympathetic activity and a reduction in parasympathetic activity [1, 2].

Many repaired (and unrepaired) congenital heart defects are associated with a variable degree of sinus node dysfunction, which may impair the chronotropic response to exercise and render them incapable of achieving a normal peak heart rate. Many antiarrhythmic medications (e.g., beta-blockers, amiodarone) also impair sinus node function. Patients with atrioventricular node disease may not be able to conduct 1:1 at higher sinus rates and therefore may be unable to achieve normal peak heart rates. Similarly, patients with pacemakers (regardless of the pacing mode) are rarely programmed to pace the ventricle at rates greater than 160 bpm.

Stroke Volume

During a progressive upright exercise test, stroke volume rises rapidly during the early phases of exercise and, at a relatively early point in the study, plateaus at a level one-and-a-half to two times greater than the baseline. (Thereafter, increases in cardiac output are due primarily to

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_2

the increases in heart rate.) Hence, peak exercise may be associated with a fivefold increase (or more) in cardiac output (HR × SV) [3–5].

The increase in stroke volume is mediated by:

1. Increased cardiac contractility secondary to increased adrenergic stimulation
2. Decreased afterload secondary to a dramatic decline in systemic and pulmonary vascular resistance during exercise
3. Enhanced ventricular filling secondary to the pumping action of the skeletal muscles [2]
4. Improved lusitropic function [6, 7]

The magnitude of the increase in contractility during exercise is not easily quantified, owing to the difficulty in obtaining the accurate and reliable noninvasive measurements required to derive preload and afterload independent indices of contractility in the setting of the tachycardia, motion, and hyperpnea associated with exercise. However, numerous studies have documented substantial enhancement of ventricular systolic performance during exercise, characterized by higher systolic tissue velocities and much more rapid ejection of larger quantities of blood over a shorter time interval, in the face of higher systolic pressures and similar ventricular end-diastolic volumes [7].

The decrease in systemic vascular resistance during exercise arises secondary to vasodilation within the exercising muscle groups (and skin) due to the release of local vasoactive substances (e.g., lactic acid and nitric oxide) and stimulation of beta receptors (while the stimulation of alpha-adrenergic receptors within the systemic resistance and capacitance vessels of the visceral organs causes blood to shunt away from these organs and toward the muscles and skin). Total peripheral resistance has been estimated to decline by 62% during exercise. This decline is associated with a remarkable redistribution of cardiac output. At rest the muscles receive only 20% of the cardiac output, whereas at peak exercise they receive 80%. The redistribution of blood flow to the muscles is also enhanced by vasoconstriction within the renal and mesenteric vascular beds during exercise [8].

The decrease in pulmonary vascular resistance is mediated by vasodilation of the pulmonary vascular bed due to the release of local vasodilators (e.g., nitric oxide), stimulation of beta-adrenergic receptors, and recruitment of vessel beds within the lung that are normally closed at rest. At rest, the lung may be divided into three zones solely on the basis of the hydrostatic pressure gradient that exists in the upright position. West Zone 3 is at the bottom of the lungs and is perfused throughout the cardiac cycle. West Zone 2 is in the middle of the lung and is perfused only during systole, and West Zone 1 is at the top of the lung and is hardly perfused at all. During exercise, pulmonary artery pressure rises, and the vascular beds that are unperfused or underperfused at rest open up [9].

The important contribution of the pumping action of the skeletal muscles to the increase in cardiac output during upright exercise is often underappreciated. This concept is illustrated by the somewhat idealized experiment (based upon work by Eugene Braunwald and others [2, 10, 11]) summarized in Table 2.1. At rest, a theoretical normal individual might have a heart rate of 60 bpm, left ventricular end-diastolic volume of 150 ml, and end-systolic volume of 50 ml. The ejection fraction would therefore be 67%, stroke volume 100 ml, and cardiac output

Table 2.1 Contribution of the pumping action of skeletal muscles to the augmentation of cardiac output during exercise

	Rest	A-pace	Isoproterenol	Exercise
HR (bpm)	60	120	120	120
LVEDV (ml)	150	100	100	150
LVESV (ml)	50	50	25	25
SV (ml)	100	50	75	125
EF (%)	67	50	75	125
C.O. (lpm)	6.0	6.0	9.0	15.0

Abbreviations: *HR* heart rate, *bpm* beats per minute, *LVEDV* left ventricular end-diastolic volume, *ml* milliliter, *LVESV* left ventricular end-systolic volume, *SV* stroke volume, *EF* ejection fraction, *C.O.* cardiac output, *lpm* liters per minute

6.0 lpm. If this subject was then atrially paced at 120 bpm, the heart would have less time to fill during diastole, and the end-diastolic volume would fall to 100 ml. End-systolic volume would not change, as the contractile state of the heart is essentially unchanged. Therefore the stroke volume and ejection fraction fall and the cardiac output is unchanged. In a second scenario, the theoretical subject is given an isoproterenol drip (a pure beta-adrenergic agonist that increases heart rate, increases contractility, and decreases systemic vascular resistance) at a rate sufficient to raise the heart rate to 120 bpm. In this scenario, left ventricular end-diastolic volume would remain lower than the baseline (due to the shorter time for ventricular filling), but the end-systolic volume would also be lower due to the increased contractility (inotropic effect) and peripheral vasodilation induced by the beta-adrenergic agonist. Hence stroke volume will be only modestly reduced compared to the baseline (the reduction is less than that associated with A-pacing), while the ejection fraction and cardiac output would be modestly increased. In a final scenario, the theoretical subject engages in upright exercise at an intensity sufficient to raise the heart rate to 120 bpm. As with isoproterenol, the end-systolic volume declines in response to the increased contractility and decreased systemic vascular resistance that accompanies exercise. Importantly, however, in this scenario, the ventricular end-diastolic volume is maintained at resting levels, despite the rapid heart rate and shorter diastolic filling time. Consequently, stroke volume, ejection fraction, and cardiac output are all substantially increased. The dramatically different hemodynamics encountered in the isoproterenol and exercise scenarios is due to the pumping action of the skeletal muscles.

The increase in stroke volume that occurs during upright exercise is related, in part, to the venous pooling that occurs in the lower extremities while in the upright position. This phenomenon does not occur during supine exercise, and consequently, the increase in stroke volume during supine exercise is much smaller (or nonexistent) [8]. It is important to bear in mind this distinction when comparing the data from disparate exercise studies employing upright vs. supine exercise protocols.

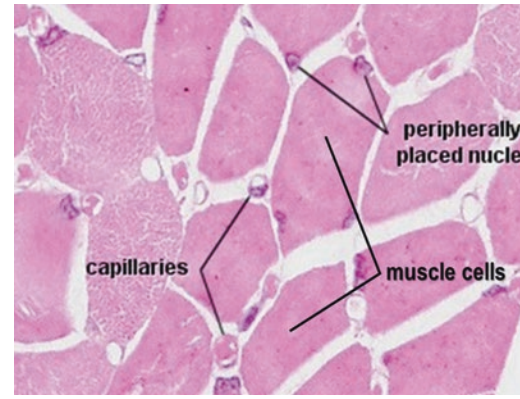


Fig. 2.1 Skeletal muscle

The source of the skeletal muscle pumping action is revealed by an analysis of the microscopic anatomy of the muscle. As can be seen in Fig. 2.1, a skeletal muscle, much like a sponge, is composed of two compartments: There is a solid component of fixed volume (the muscle fibers themselves) and a fluid-filled component of variable volume (the rich vascular bed that surrounds each muscle fiber). When a muscle contracts, the fibers shorten. Since the fiber volume is fixed, the diameter of the fiber increases as the fiber shortens. The fiber therefore bulges into and compresses the vascular space around the fiber, effectively squeezing the blood from the surrounding vascular space, into the low-pressure, high-capacitance veins, toward the heart. When the muscle relaxes, the recoil of the muscle fiber draws blood from the high-pressure arteries into the capillaries. Hence the contraction of the skeletal muscles enhances venous return to the heart, and the relaxation of the muscles acts as the perfect afterload-reducing agent, facilitating ejection of blood from the left ventricle and promoting forward cardiac output. One can envision that the importance of the skeletal muscle's pumping action to the cardiovascular response to

exercise may be magnified in some of the pathophysiologic conditions encountered in patients with congenital heart disease (e.g., patients without a subpulmonary ventricle).

Enhanced lusitropic (diastolic) function of the ventricle is another important component of the cardiopulmonary response to exercise. During exercise, the ventricle must fill much more rapidly than it does at rest; the cardiac output is much higher, and the time available to fill the ventricle (diastole) is much shorter. Rapid ventricular filling is promoted by the increase in left atrial pressure that normally occurs during exercise. In addition, in the setting of adrenergic stimulation, postsystolic calcium reuptake by the myocardial cell's sarcoplasmic reticulum is enhanced. This, in combination with the increased contractility (and consequent increased stretching of series elastic elements within the myocardial muscle fibers), results in an elastic recoil that can actually produce a negative pressure within the left ventricle in early diastole and help enhance blood flow into the left ventricle from the left atrium and pulmonary veins [6].

Oxygen Extraction

In normal individuals at rest, arterial oxygen saturation approaches 100%, and mixed venous oxygen saturation is approximately 70%. Hence, the body extracts only 30% of the oxygen delivered to it. At peak exercise, however, the exercising muscles extract a much greater percentage of the oxygen delivered to them. Mixed venous oxygen saturation typically falls to less than 30%, and the total body oxygen extraction more than doubles at peak exercise. Several factors contribute to the increased oxygen extraction during exercise. This physiology is best understood by consideration of the concept of *flux*; i.e., the amount of a substance (in this case, oxygen) that flows across a membrane (in this case, between the capillary and the muscle cell) per unit area and per unit of time. Flux is determined by the concentration gradient as well as the permeability and area of the membrane. Each of these variables changes during exercise so that the oxygen flux is enhanced. Exercise is associated with the recruitment and vasodilation of capillary beds close to the metabolically active muscle cells. The vasodilation and recruitment of capillary beds within the muscle is mediated by the stimulation of beta-adrenergic receptors within vascular beds, as well as the accumulation of vasoactive substances, such as lactic acid and nitric oxide, locally within the muscle. Consequently there is a larger surface area across which oxygen may diffuse into the muscle cells and a shorter distance between the oxygen-bearing red blood cells within the capillaries and the oxygen-consuming mitochondria within the muscle cells. In addition, pO_2 (partial pressure of oxygen) within the muscle cells declines during exercise, resulting in an increased oxygen tension gradient between the blood and the muscle. These anatomic and physiologic changes facilitate and enhance the flow of oxygen from the blood to the muscles [12].

The accumulation of lactic acid within the muscle (secondary to anaerobic metabolism) also facilitates the release of oxygen from hemoglobin. This phenomenon, known as the "Bohr effect," is a consequence of the rightward shift of the hemoglobin-oxygen dissociation curve in acidic environments. When the pH within the muscle falls (due to the accumulation of lactic acid at higher intensities of exercise), oxygen binds less tightly to hemoglobin and is more readily released from hemoglobin to the muscle [12].

Exercise may also be associated with a degree of hemoconcentration, secondary to the loss of extracellular fluid through perspiration and the shift of fluid from the extracellular to the intracellular space due to an increase of intracellular osmolarity associated with the generation of lactate and other osmotically active metabolic byproducts. These phenomena will increase the hemoglobin concentration and the oxygen-carrying capacity of the blood [13].

An autotransfusion of red blood cells into the circulation secondary to splenic contraction in response to catecholaminergic stimulation may also boost hemoglobin concentration during exercise. A normal adult's spleen contains ~250 ml of blood with a hematocrit more than twice as high as that found in arterial blood. In response to adrenergic stimulation, the splenic

capsule (which is rich in alpha-adrenergic receptors) contracts, and up to 56% of this "splenic reservoir" may be added to the circulation, raising the hemoglobin levels by 2–6% [14, 15].

Hence, from consideration of Fick equation, it can be seen that the cardiovascular adaptations to exercise permit the oxygen consumption at peak exercise to increase more than tenfold over the resting values.

Kinetics of Oxygen Delivery and Oxygen Debt

At the start of exercise and as exercise intensity increases, oxygen delivery to the exercising muscles does not immediately increase in conjunction with the increased metabolic demands of the muscles; there is a time interval during which the adenosine triphosphate (ATP) requirements of the muscle exceed that which can be derived from aerobic metabolism. During this time interval, the muscle cells must rely on endogenous stores of ATP, creatine phosphate, and other high-energy moieties to provide the energy required to perform the mechanical work of exercise. This time lag increases at higher exercise intensities, and at intensities beyond the VAT (ventilatory anaerobic threshold), oxygen delivery may never meet the muscles' energy requirements. After the termination of exercise, $\dot{V}_{O2}$ remains elevated for a period of time (even though the mechanical work of exercise has ceased) in order to "repay" this oxygen debt, replenish the muscle cell energy stores, metabolize the lactate that has accumulated, and restore the normal lactate/pyruvate and $NADH_2^+/NAD^+$ ratios. Patients with impaired cardiac outputs accumulate an oxygen debt more rapidly and repay it more slowly [16, 17].

Acknowledgment Portions of this chapter were based upon the author's previously published works:

- Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.
- Rhodes J. Exercise testing. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Elsevier; 2006.

References

1. Rhodes J. Exercise testing. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. Philadelphia: Elsevier; 2006. p. 275–87.
2. Braunwald E, Sonnenblick EH, Ross J Jr, Glick G, Epstein SE. An analysis of the cardiac response to exercise. Circ Res. 1967;XXII(Suppl 1):I-44-I-58.
3. Lavie CJ, Arena R, Swift DL, Johannsen NM, Sui X, Lee DC, et al. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. Circ Res. 2015;117(2):207–19.
4. Ekelund LG, Holmgren A. Central hemodynamics during exercise. Circ Res. 1967;20 and 21(Suppl I):I-33-I-43.
5. Loeppky JA, Greene ER, Hoekenga DE, Caprihan A, Luft UC. Beat-by-beat stroke volume assessment by pulsed doppler in upright and supine exercise. J Appl Physiol Respir Environ Exerc Physiol. 1981;50(6):1173–82.
6. Udelson JE, Bacharach SL, Cannon RO III, Bonow RO. Minimum left ventricular pressure during beta-adrenergic stimulation in human subjects. Evidence for elastic recoil and diastolic "suction" in the normal heart. Circulation. 1990;82(4):1174–82.
7. Rowland T. Echocardiography and circulatory response to progressive endurance exercise. Sports Med. 2008;38(7):541–51.
8. Laughlin MH, Davis MJ, Secher NH, van Lieshout JJ, Arce-Esquivel AA, Simmons GH, et al. Peripheral circulation. Compr Physiol. 2012;2(1):321–447.
9. Naeije R, Chesler N. Pulmonary circulation at exercise. Compr Physiol. 2012;2(1):711–41.
10. Ross JL, Linhart JW, Braunwald E. Effects of changing heart rate in man by electrical stimulation of the right atrium. Circulation. 1965;62:528–34.
11. Bada AA, Svendsen JH, Secher NH, Saltin B, Mortensen SP. Peripheral vasodilatation determines cardiac output in exercising humans: insight from atrial pacing. J Physiol. 2012;590(8):2051–60.
12. Wasserman K, Hansen DA, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. Philadelphia: Lippincott, Williams & Wilkins; 1999.
13. Senay LC Jr, Pivarnik JM. Fluid shifts during exercise. Exerc Sport Sci Rev. 1985;13:335–87.
14. Shephard RJ. Responses of the human spleen to exercise. J Sports Sci. 2016;34(10):929–36.
15. Stewart IB, McKenzie DC. The human spleen during physiological stress. Sports Med. 2002;32(6):361–9.
16. Cohen-Solal A, Laperche T, Morvan D, Geneves M, Caviezel B, Gourgon R. Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure. Analysis with gas exchange measurements and NMR spectroscopy. Circulation. 1995;91(12):2924–32.
17. Tanabe Y, Takahashi M, Hosaka Y, Ito M, Ito E, Suzuki K. Prolonged recovery of cardiac output after maximal exercise in patients with chronic heart failure. J Am Coll Cardiol. 2000;35(5):1228–36.

3 Central Hemodynamics and Coronary Blood Flow During Exercise

Jonathan Rhodes

Knowledge of the normal hemodynamic changes associated with exercise is essential to the understanding of exercise physiology. Systolic blood pressure rises progressively as exercise intensity increases. With dynamic exercise, systolic pressures between 30% and 60% above resting values are typically encountered at peak exercise. During a progressive exercise test, an increase in systolic blood pressure at a peak exercise of <20 mm Hg or <20% above resting values is considered a blunted response. In adult males, a systolic blood pressure greater than 210 mm Hg is considered abnormal; in adult females, the upper limit of normal is 190 mm Hg. Systolic blood pressures tend to be lower in children and adolescents. In adolescent males and females, systolic blood pressure rarely exceeds 180 and 160 mm Hg, respectively, at peak exercise. Somewhat lower values are encountered in children (Fig. 3.1). Diastolic blood pressure changes little during dynamic exercise [1]. Mean systemic blood pressure typically rises ~30% [2]. Systolic blood pressures exceeding 300 mm Hg and diastolic pressures exceeding 200 mm Hg may be encountered during intense isometric exercise [3].

Pulmonary artery systolic pressure may double during dynamic exercise, from baseline, resting levels of 20–25 mm Hg to as high as 50 mm Hg at higher levels of exercise. The rise in pulmonary artery systolic pressure during exercise facilitates the recruitment of capillary beds in the middle and toward the apices of the lungs (West Zones 1 and 2). Mean pulmonary artery pressure also rises from ~12–15 mm Hg to ~25 mm Hg. The rise in mean pulmonary artery pressure is accompanied by an almost equivalent rise in the mean pulmonary capillary wedge pressure, as the left ventricle moves up its Starling curve to accommodate the hemodynamic demands of exercise. Hence, the transpulmonary gradient increases only modestly during exercise (Fig. 3.2) [2]. Since exercise is associated with a >5-fold increase in cardiac output, a dramatic decline in pulmonary vascular (arteriolar) resistance, to levels ~40% of those present at rest, may be inferred [2, 4].

In contrast to the left-sided filling pressures, exercise has little effect upon right atrial and right ventricular end-diastolic pressures [2, 4]. The systemic vascular resistance—i.e., mean arterial pressure minus mean right atrial pressure, divided by systemic blood flow—therefore falls almost as much as the pulmonary vascular resistance. This decline is due to vasodilation within the exercising muscles, as well as the pumping action of the skeletal muscles described in Chap. 2.

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_3

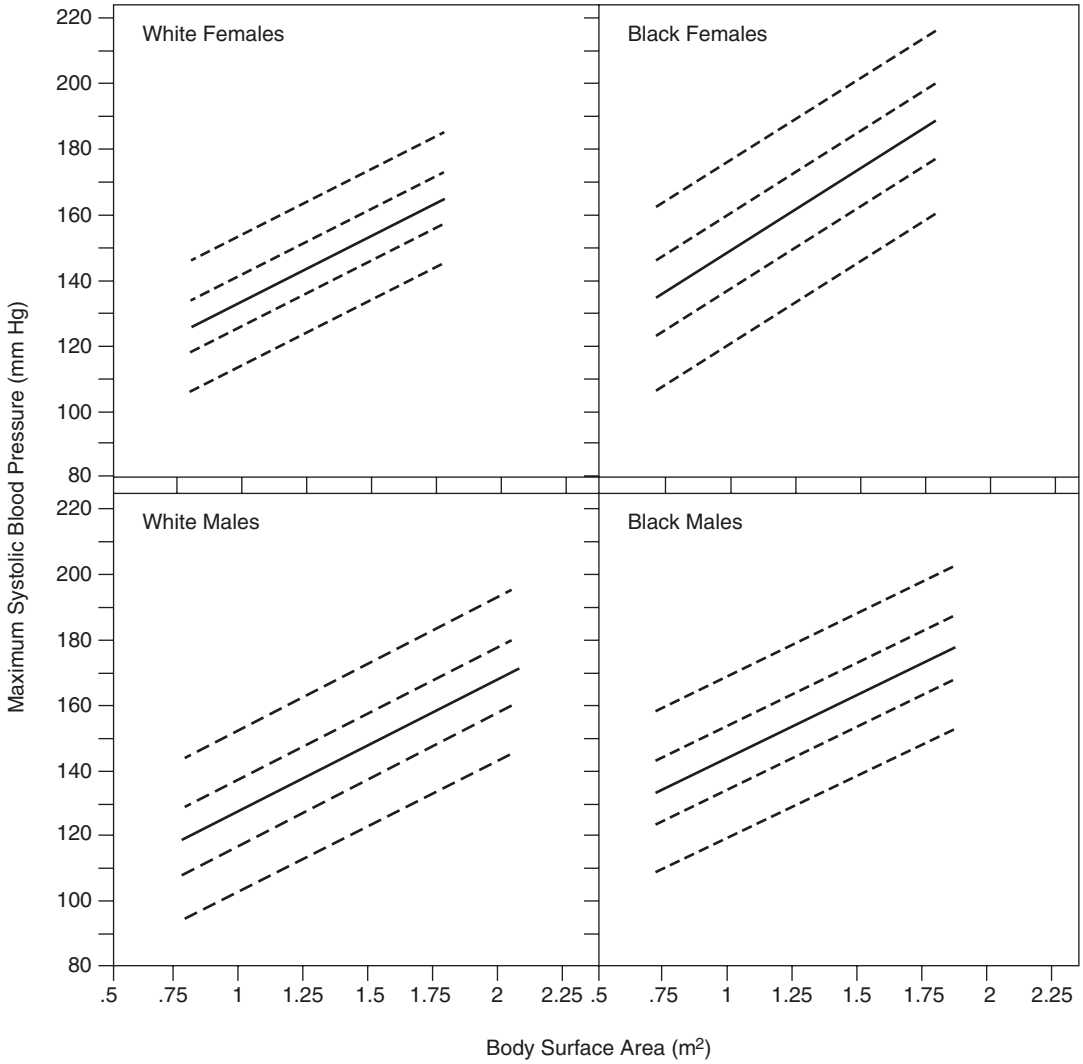


Fig. 3.1 Nomograms of maximum systolic blood pressure (mm Hg) against body surface area. The solid line is the regression line; the dashed lines represent the 5th, 25th, 75th, and 95th percentile prediction limits. (Reprinted with permission from [1])

From these considerations, it may also be seen that, while the right ventricle performs less work (i.e., pressure × volume) than the left ventricle, the percentage increase in workload assumed by the right ventricle and the percentage increase in potential energy imparted to the blood by the right ventricle (mean pulmonary artery pressure minus mean right atrial pressure) during exercise substantially exceed the corresponding contributions by the left ventricle. This physiology may have particularly important implications for congenital heart lesions where there is an abnormal, or even absent, right ventricle.

To perform the additional work required by exercise, myocardial oxygen consumption and myocardial oxygen supply (i.e., coronary blood flow) must increase dramatically. However, because of the elevated intramyocardial pressures that occur during systolic contraction, coronary artery blood flow (80% of the blood flow to the left or systemic ventricle) occurs primarily during diastole. Moreover, diastole occupies a smaller and smaller fraction of the cardiac cycle as heart rate rises. These challenges are overcome, in part, by vasodilation of the coronary vascular beds in response to changes in autonomic tone, systemic,

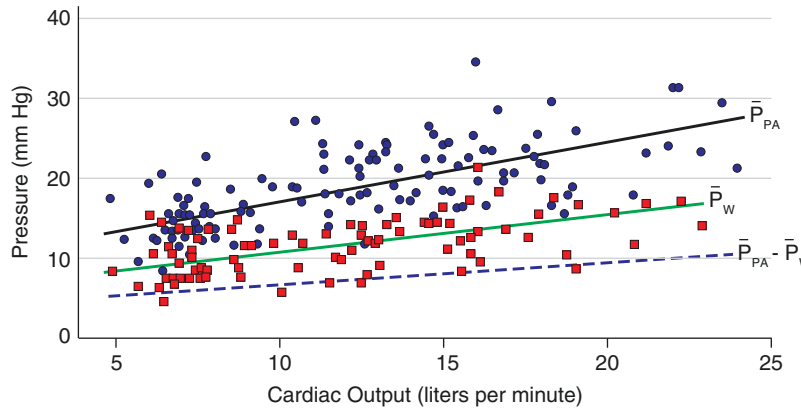


Fig. 3.2 Changes in cardiac output, mean pulmonary artery pressure (P_{PA}, black line), pulmonary capillary wedge pressure (P_W, green line), and transpulmonary gradient (P_{PA}-P_W, dotted blue line) during exercise. Note that the fivefold increase in cardiac output is associated with only a modest increase in transpulmonary gradient. Blue dots represent mean pulmonary artery pressure and red squares represent mean pulmonary capillary wedge pressure. (Adapted and based on data from [2])

and local vasoactive mediators [5, 6]. As with skeletal muscles, another important (and underappreciated) factor promoting the augmentation of coronary blood flow during exercise is a "sponge effect." Histologic studies demonstrate that the myocardium also has a "sponge-like" structure, i.e., a fixed-volume muscle fiber component embedded in a rich vascular network of variable volume [7]. Under normal circumstances, this vascular volume may comprise as much as 13% of the myocardial volume [7]. Each time the myocardium contracts, the intramyocardial vascular volume is compressed, and blood is squeezed out of the myocardium toward the low-pressure coronary veins and coronary sinus. When the myocardium relaxes, the vascular space is refilled by flow from the high-pressure coronary arteries. Moreover, when myocardial muscle fibers contract, they displace blood from the vascular space in the closest proximity to the muscle fibers. Over the course of the cardiac cycle, the myocardial cells exchange gases and metabolites most extensively with the blood in this vascular space. Hence, when blood is expelled from the myocardium during systole, the metabolically important vascular space closest to the muscle fibers is emptied and is then efficiently replenished with fresh coronary arterial blood during the subsequent diastole.

Consistent with this picture, while the flow within the coronary arteries (especially the arteries supplying the left ventricle) has been found to occur primarily during diastole, the flow in the coronary sinus occurs primarily during systole [5–7]. Thus the increased heart rate associated with exercise facilitates the increase in coronary blood flow by increasing the times per minute that the coronary capillaries are mechanically compressed (emptied) and refilled. The increase in ventricular systolic pressure and ventricular contractility that is associated with exercise also promotes coronary blood flow by compressing and emptying the coronary capillaries more thoroughly with each cardiac contraction. In this manner, the increased myocardial oxygen consumption associated with exercise is promptly and closely matched by a concomitant increase in coronary blood flow.

The STT changes encountered in patients who develop myocardial ischemia during exercise (ST depression and/or T wave inversions) often resemble those seen in patients with dilated cardiomyopathy. It is tempting to speculate that a similar physiology—i.e., an imbalance between myocardial oxygen consumption and myocardial oxygen delivery—underlies both observations. In patients with myocardial ischemia, stenoses within the coronary arteries limit the delivery of blood and oxygen to the myocardium, and an imbalance develops when myocardial oxygen consumption increases during exercise and the

coronary blood flow cannot increase to meet this demand. In patients with dilated cardiomyopathy, increased myocardial oxygen consumption due to elevated myocardial wall stress (secondary to ventricular dilation and decreased ventricular wall thickness) and decreased oxygen delivery due to diminished compression of the myocardial vascular space during each cardiac cycle (due to the contractile dysfunction) are factors that may contribute to a chronic imbalance between oxygen delivery and oxygen demand.

Acknowledgment Portions of this chapter were based upon the author's previously published works:

- Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010; 122(19):1957–67.
- Rhodes J. Exercise testing. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Elsevier; 2006.

References

1. Alpert BS, Flood NL, Strong WB, Dover EV, DuRant RH, Martin AM, et al. Responses to ergometer exercise in a healthy biracial population of children. J Pediatr. 1982;101(4):538–45.
2. Ekelund LG, Holmgren A. Central hemodynamics during exercise. Circ Res. 1967;20 and 21(Suppl I):I-33-I-43.
3. Palatini P, Mos L, Munari L, Valle F, Del Torre M, Rossi A, et al. Blood pressure changes during heavy-resistance exercise. J Hypertens Suppl. 1989;7(6):S72–3.
4. Naeije R, Chesler N. Pulmonary circulation at exercise. Compr Physiol. 2012;2(1):711–41.
5. Braunwald E. Control of myocardial oxygen consumption: physiologic and clinical considerations. Am J Cardiol. 1971;27(4):416–32.
6. Goodwill AG, Dick GM, Kiel AM, Tune JD. Regulation of coronary blood flow. Compr Physiol. 2017;7(2):321–82.
7. Spaan JA. Mechanical determinants of myocardial perfusion. Basic Res Cardiol. 1995;90(2):89–102.

CO_2 Elimination ($\dot{V}_{CO2}$)

4

Jonathan Rhodes

During exercise, CO_2 production by the muscles increases dramatically. The CO_2 is transported from the muscles to the lungs via the bloodstream. Two mechanisms permit the efficient transport of the increased quantities of CO_2: (1) as discussed in Chap. 2, cardiac output may increase more than fivefold during exercise; and (2) venous CO_2 content rises during exercise. Unlike oxygen, CO_2 is very soluble in blood. In the physiologic range, the CO_2 content is approximately proportional to the partial pressure of CO_2 (pCO_2). Mixed venous pCO_2 levels may increase from 42–45 mm Hg at rest to as much as 60 mm Hg (or more) at peak exercise [1]. When applied to the question of CO_2 elimination, the Fick equation indicates that $\dot{V}_{CO2}$ is equal to the cardiac output (or equivalently, the pulmonary blood flow) times the pulmonary arterial (or equivalently, the mixed venous)–pulmonary venous CO_2 content difference:

$$\dot{V}_{CO2} = PBF \times \left(C_{PA}CO_2 - C_{PV}CO_2 \right)$$

One can therefore readily appreciate that the exercise-related increases in cardiac output and mixed venous CO_2 content can result in as much as a 20-fold increase in $\dot{V}_{CO2}$ at peak exercise.

Homeostatic mechanisms, based upon an afferent limb from chemoreceptors in the aortic arch (and elsewhere?) to the respiratory center in the medulla oblongata and an efferent limb from the respiratory center to the diaphragm and muscles of respiration, maintain arterial pH at 7.40 [2–4]. In the absence of a metabolic acidosis or alkalosis, this requires respiration during exercise to be adjusted so as to maintain arterial pCO_2 (which in healthy individuals is equivalent to alveolar and/or pulmonary venous pCO_2) at 40 mm Hg. The respiratory adaptations that allow for the robust increase in CO_2 excretion by the lungs, while maintaining normal arterial pCO_2, are best understood from the equation:

$$\dot{V}_{CO2} = \dot{V}_A \times \left(P_A CO_2 / P_B \right) \qquad (4.1)$$

This equation simply states that $\dot{V}_{CO2}$ is equal to the alveolar ventilation times the partial pressure of CO_2 within the alveolus divided by barometric pressure (P_B).

Alveolar ventilation is equal to minute ventilation minus dead space ventilation ($\dot{V}_A = \dot{V}_E - \dot{V}_D$). Substitution into the above equation yields:

$$\dot{V}_{CO2} = \left(\dot{V}_E - \dot{V}_D \right) \times \left(P_A CO_2 / P_B \right) \qquad (4.2)$$

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_4

Minute ventilation equals respiratory rate (RR) times tidal volume, and dead space ventilation equals RR times dead space volume:

$$\dot{V}_{CO2} = RR \times \left(V_T - V_D\right) \times \left(P_A CO_2 / P_B\right) \quad (4.3)$$

$$= RR \times V_T \left(1 - V_D / V_T\right) \times \left(P_A CO_2 / P_B\right) \quad (4.4)$$

The manner in which each of these respiratory variables is adjusted to accommodate the increased $\dot{V}_{CO2}$ during exercise will now be discussed.

Tidal Volume

During a progressive exercise test, a rapid increase in tidal volume is typically seen during the early phases of exercise. At higher levels of exercise, additional increases in tidal volume are relatively small, and most of the augmentation of ventilation that occur results from the increases in respiratory rate. Typically, the tidal volume at peak exercise increases approximately threefold over baseline values, to approximately 45–65% of a subject's baseline forced vital capacity.

Respiratory Rate

During a progressive exercise test, the respiratory rate tends to increase slowly at lower levels of exercise and more rapidly at higher exercise intensities. At peak exercise, the respiratory rate typically increases to three or four times resting values. In normal individuals (beyond childhood), however, it rarely exceeds 60 breaths per minute.

V_D/V_T Ratio

During exercise, the anatomic dead space volume remains fixed, whereas the tidal volume increases dramatically; the V_D/V_T ratio therefore falls. Moreover, as one exercises and recruits more blood vessels in the West zones 1 and 2 (in the upper parts of the lungs), ventilation/perfusion matching improves, physiologic dead space declines, the V_D/V_T ratio declines, gas exchange becomes more efficient, and CO_2 elimination is enhanced.

Hence, from Eq. 4.4 above, it can be seen that the respiratory adaptations to exercise permit the $\dot{V}_{CO2}$ at peak exercise to increase more than 12-fold over resting values.

Anaerobic Threshold: Implications for CO_2 Elimination (and Oxygen Delivery)

During the course of a progressive exercise test, one may come to a point where $\dot{V}_{CO2}$ begins to increase out of proportion to the concomitant increase in oxygen consumption. If one were to obtain blood samples at this time, one would also observe an increase in the lactate levels. This point has been named the "anaerobic threshold." Theoretically, it reflects the point during a progressive exercise test when the amount of adenosine triphosphate (ATP) required by the muscles to perform the mechanical work of exercise exceeds that which may be produced solely via aerobic metabolism (which is limited by the amount of oxygen that can be delivered to the muscles by the cardiopulmonary system). The muscle cells then begin to rely upon anaerobic metabolism to generate a portion of the ATP they require [5–7]. As noted in Chap. 1, anaerobic metabolism does not consume oxygen, but it does produce lactic acid, which is buffered by bicarbonate to produce CO_2. This physiology explains the disproportionate increase in $\dot{V}_{CO2}$ and the rise in serum lactate levels that are observed.

Equation 4.1 indicates that to maintain a normal pH in the face of this increased CO_2 production, alveolar ventilation must rise proportionately. Moreover, as exercise continues above the anaerobic threshold, lactate levels rise further and a metabolic acidosis develops. To maintain a normal pH under these circumstances, the respiratory system must generate a compensatory respiratory alkalosis; that is, arterial pCO_2 (which in healthy people is approximately equivalent to alveolar pCO_2) must be driven down. Equation 4.1 also indicates that, at any level of $\dot{V}_{CO2}$, a dec-

rement in alveolar pCO_2 must be matched by a reciprocal increase in alveolar ventilation. Hence, exercise beyond the anaerobic threshold requires increased ventilation because of: (1) increased $\dot{V}_{CO2}$ secondary to increased aerobic metabolism of fuels; (2) increased CO_2 production related to anaerobic metabolism and the buffering of lactic acid by bicarbonate (detected at the anaerobic threshold); and (3) the need to blow off CO_2 and generate a respiratory alkalosis to compensate for the accumulating lactic acidosis. The point where the compensatory respiratory alkalosis begins to develop has been termed the "respiratory compensation point."

The lactic acid produced by anaerobic metabolism also has profound implications for oxygen delivery to the muscles. As discussed in Chap. 3, lactic acid promotes the release of oxygen to the muscles by shifting the hemoglobin-oxygen dissociation curve to the right (the Bohr effect). The acidic environment produced by lactic acid also promotes vasodilation of blood vessels within the exercising muscles, thereby allowing more oxygen-rich blood to come into close proximity with the exercising, metabolically active muscle cells. (It seems that God did not create lactic acid because s/he is a sadist, but to provide a mechanism for prey species to generate extra energy when needed to escape predators, and vice versa!)

Acknowledgment Portions of this chapter were based upon the author's previously published works:

- Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.
- Rhodes J. Exercise testing. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Elsevier; 2006.

References

1. Jones NL. Clinical exercise testing. 4th ed. Philadelphia: W. B. Saunders; 1997.
2. Whipp BJ, Ward SA, Wasserman K. Ventilatory responses to exercise and their control in man. Am Rev Respir Dis. 1984;129(2 Pt 2):S17–20.
3. Wasserman K, Cox TA, Sietsema KE. Ventilatory regulation of arterial h(+) (ph) during exercise. Respir Physiol Neurobiol. 2014;190:142–8.
4. Sietsema KE, Cooper DM, Perloff JK, Child JS, Rosove MH, Wasserman K, et al. Control of ventilation during exercise in patients with central venous-to-systemic arterial shunts. J Appl Physiol. 1988;64(1):234–42.
5. Wasserman K. Determinants and detection of anaerobic threshold and consequences of exercise above it. Circulation. 1987;76(Supp VI)(6:Pt 2)):VI-29-VI-39.
6. Wasserman K. The Dickinson w. Richards lecture. New concepts in assessing cardiovascular function. Circulation. 1988;78(4):1060–71.
7. Wasserman K. The anaerobic threshold measurement to evaluate exercise performance. Am Rev Respir Dis. 1984;129(2:Pt 2):t-40.

Part II

Conduct of the Cardiopulmonary Exercise Test

Laboratory Setup, Equipment, and Protocols

5

Julieann O'Neill and Laura Bourette

Environment

A pediatric exercise laboratory should have sufficient space to comfortably accommodate the equipment described as follows. It should also have space for the parents of the patient to sit during the test. The temperature should be maintained in the range of 20 °C (68 °F) to 24 °C (75 °F) with a relative humidity between 50% and 60% [1].

Equipment

The exercise lab should be equipped with devices that can accommodate both pediatric and adult patients. The equipment required by a modern laboratory includes [1–3]:

1. *A cycle ergometer*. Two types of cycle ergometers exist, distinguished by the manner in which the imposed work rate is controlled. Mechanically braked cycle ergometers control external work rate through frictional bands, whereas electronically braked ergometers increase resistance to pedaling electromagnetically. Electronically braked cycle ergometers are preferred, as they provide a reliable, constant work rate across a wide range of pedaling speeds. The cycle ergometer should be equipped with an adjustable seat, pedals, and handlebars, allowing the device to accommodate both children and adults.
2. *A motorized treadmill*. The treadmill should be equipped with front and side handrails at heights appropriate for children and adults. It should also be equipped with an emergency stop button that is readily accessible to the individual(s) conducting the test.
3. *Electrocardiographic (EKG) monitoring equipment*. The EKG recording equipment should have a real-time display screen and a printer capable of providing prompt, real-time printouts of 12-lead EKGs and/or rhythm strips for review. The display screen should be large enough and positioned so that it can be seen easily by the testing personnel during the study. It should display at least three EKG leads in real time. The displayed leads should be adjustable, to permit optimal visualization of the P waves or STT changes, as necessary. A numeric display of the heart rate should also be included on the screen. Instantaneous "superimposition" scanning of median EKG complexes from selected leads is a worthwhile feature that can facilitate real-time detection of STT changes during exercise. A printout of

J. O'Neill (✉)
Exercise Physiology, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: julieann.oneill@cardio.chboston.org

L. Bourette
Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_5

the median EKG complexes at each stage can also help with the analysis by a subsequent interpreter. A computer-based recording system can also provide a "full-disclosure" review of EKG waveforms during a study. This feature permits review of rhythm, STT, or morphology changes that may not have been acquired on paper EKG recordings.

4. *A metabolic cart*. Over the past two decades, commercially available metabolic carts have become standard equipment in most pediatric exercise laboratories. Breath-by-breath, rather than mixing chamber, systems are preferable because of their ability to simultaneously measure end-tidal pCO_2 and pO_2, as well as their ability to rapidly and flexibly process data and display the data in various formats and at various time intervals. The metabolic cart should be equipped with software that permits the acquisition of basic spirometric measurements, as these measurements are integral to the interpretation of some of the metabolic cart data. Software that provides the option to acquire exercise flow volume loop acquisition is also worthwhile.

   Modern metabolic carts are generally reliable, economical, and easy to maintain. They should be equipped with pediatric and adult-sized mouthpieces (and appropriate nose clips) and/or face masks. Most patients find the mouthpiece-nose clip combination to be more comfortable. It is also easier to maintain an airtight seal with a mouthpiece-nose clip combination. However, an occasional patient with an exaggerated gag reflex will prefer a mask rather than a mouthpiece. The metabolic cart should be interfaced with the treadmill, cycle ergometer, and EKG monitoring system. Ideally, it should also interface with the hospital's database, thereby allowing the exercise test data to be imported directly and accurately into an individual patient's hospital record or database.
5. *Blood pressure cuffs*. Although a number of automated blood pressure monitoring systems have been developed, their reliability is adversely affected by the noise and movement that accompany an exercise test. Consequently, direct auscultation by a well-trained individual probably remains the most reliable and accurate method for determining the blood pressure during exercise. A good-quality stethoscope and appropriate-sized blood pressure cuffs should be available.

   For patients with aortic coarctation (repaired or unrepaired) and other aortic arch surgery (e.g., interrupted aortic arch, hypoplastic left heart syndrome, etc.), determination of upper and lower extremity blood pressures, before and after exercise, may be an important component of the exercise test. Pediatric exercise laboratories should therefore also be provided with appropriate thigh-sized blood pressure cuffs.
6. *A pulse oximeter*. Fingertip or ear lobe pulse oximeters are generally available. In some patients with congenital heart disease, the blood flow to an extremity may be compromised by the congenital defect and/or subsequent surgical interventions. Therefore, when using a fingertip oximeter, it is important to ascertain that an accurate pulse oximetry reading can be obtained from that extremity prior to initiating the exercise test. It may also be necessary to remove a patient's fingernail polish prior to the test. Tightly gripping the support bars or handlebars of the ergometer may also interfere with the function of the fingertip oximeter, and it may be necessary to ask the patient to temporarily release the bar to obtain an accurate reading. Ear jewelry may interfere with the function of an earlobe oximeter and should be removed prior to testing. Ensuring adequate surface contact and perfusion will improve the pulse oximeter reliability. Gently rubbing the lobe to improve local perfusion may also be helpful. When a pulse oximeter is functioning properly, it should have a good waveform, and the heart rate detected by the oximeter should match the heart rate detected by the EKG monitor.
7. *Other equipment*. The exercise laboratory should be configured with sufficient space for stress echocardiography to be performed (when necessary) and for the patient to be able to move quickly and safely from the cycle or

treadmill to the echocardiography bed. Space for other equipment, such as noninvasive cardiac output devices, near-infrared spectroscopy machines, blood sampling, and/or injection of radioisotopes for nuclear medicine tests, should also be available.

8. *Safety equipment*. A fully stocked and well-maintained code cart with a defibrillator and medications appropriate for pediatric and adult-sized patients, as well as a bed with access to oxygen and suction, should be available within the laboratory. A "code button" or other device capable of promptly summoning assistance when necessary should also be readily accessible.

Protocols

The 6-Minute Walk Test (6MWT)

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 meters (or 100 feet) 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 [4]. Portable pulse oximetry may be incorporated into the test, but the patient's heart rhythm and electrocardiogram are (usually) not monitored, unless portable telemetry is available.

The advantages of 6MWT are that it is easy to perform, does not require sophisticated equipment, and mimics activities of daily living [4]. 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 6MWT correlates fairly well with peak oxygen consumption in highly symptomatic patients, its utility and validity in patients with "only" mild or moderate impairments are dubious [5]. Indeed, some investigators have questioned the reliability and meaning of 6MWT for patients that can walk more than 400 meters [6]. In addition, the test is strongly influenced by patient motivation and other factors (such as leg length, body weight, orthopedic issues, the ability to turn quickly at the ends of the course, etc.) unrelated to the cardiopulmonary system. It is difficult to control and/or quantify the influence of these variables on the outcome variable (distance walked) of 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 one individual) ambiguous and difficult. On account of these considerations, the utility of 6MWT in children with congenital heart disease is limited.

Finally, although the incidence of serious adverse events during 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 Electrocardiographic Monitoring

Exercise testing may be undertaken in conjunction with 12-lead EKG monitoring. A blood pressure cuff and, when indicated, pulse oximetry probe are also applied. Depending upon the clinical issues being addressed by the exercise test, other diagnostic modalities may be added to the exercise stress test, including myocardial perfusion imaging, stress echocardiography, and pre-/postexercise spirometry. The Bruce treadmill protocol is the exercise protocol that is commonly employed for these tests [1, 7]. In this protocol, the speed and elevation of the treadmill are increased in stages, in a standardized, predetermined manner, every 3 minutes. The patient is encouraged to walk or, at higher stages, jog/run on the treadmill for as long as she/he can. The protocol has seven stages, so theoretically the test cannot last for more than 21 minutes, although for extremely fit individuals who do not reach their limit within 21 minutes, the seventh stage can be extended, or additional non-

standard stages may be added. The endurance time (i.e., the time until the patient stops exercising) is used as an index of exercise capacity. Nomograms are available for calculating the predicted, normal endurance time [7]. For pediatric subjects, the normal range is quite broad, however, and the clinical utility of this metric is therefore somewhat limited. Endurance time is also heavily influenced by factors unrelated to the cardiopulmonary system (e.g., obesity, orthopedic issues, etc.), and this metric therefore may not provide reliable, unambiguous information regarding 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 may not reflect a maximal effort expenditure. Similarly, the peak heart rate may not accurately reflect whether or not a patient has expended a maximal effort, as many patients with postoperative congenital heart disease have sinus node dysfunction and/or are on medications that may impair the chronotropic response to exercise. Hence, in children and patients with CHD, the ability of exercise testing with EKG monitoring to provide objective, quantitative data regarding a patient's exercise capacity is suboptimal. In addition, this testing modality often provides little information regarding the factors that may be responsible for a CHD patient's exercise intolerance [8, 9].

Exercise testing with EKG 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 [1]. For pediatric subjects with congenital heart disease, the presence, or absence, of exercise-induced STT abnormalities in isolation is not particularly helpful with regard to the question of myocardial ischemia, due to the high prevalence of intraventricular conduction delays and other baseline abnormalities, the low pretest probability, and the absence of normative data [9, 10].

Similarly, for pediatric patients with chest pain, the probability of a cardiac etiology is extremely low and the ability of an exercise EKG to detect an abnormality is uncertain. Consequently, a positive test is likely to be a false-positive, and a negative test is virtually meaningless (Bayes' theorem). The role of exercise testing in this setting has therefore been questioned [11–14]. In this clinical setting, however, exercise testing with pre- and postexercise spirometry may be worthwhile for the evaluation of possible exercise-induced asthma (see later)—a much more common cause of exertional chest pain [12].

The treadmill speeds used for the higher levels of the Bruce protocol may be too fast for small children. Under these circumstances, alternative protocols may be employed. For very limited patients, a "modified" Bruce protocol (in which 3 minute stages at 0% and 5% grades and speeds of 1.7 mph are introduced prior to the standard first stage) may be employed, although interpretation of endurance time then becomes even more problematic. Alternatively, bicycle protocols may also be used [1]. 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 based upon a patient's age, gender, and size. Some of the limitations associated with the use of the treadmill endurance time as an index of cardiopulmonary function (e.g., the difficulty ascertaining whether or not a child has expended an optimal effort) also apply to the peak work rate.

Cardiopulmonary Exercise Testing (CPET)

In addition to the data obtained on standard exercise test with EKG monitoring, a cardiopulmonary exercise test (CPET) acquires data from expiratory gas (metabolic cart) analyses. Most modern metabolic carts measure the volume of gas expired by the patient, on a breath-by-breath basis, along with the instantaneous CO_2 and O_2 concentrations. From these data, moment-by-moment estimates of minute ventilation, carbon dioxide production, and oxygen consumption can

be calculated. End-tidal pCO_2 and O_2 levels can also be measured. A wealth of clinically valuable information can be derived from these data (see Chaps. 11 and 12). This information often provides the most comprehensive, objective, and quantitative assessment of an individual's exercise capacity, cardiopulmonary response to exercise, and the factor(s) that limit exercise function. CPET is therefore the testing modality that is, in general, most appropriate for patients with congenital heart disease and many other cardiovascular and/or pulmonary disorders [3, 10].

CPET studies may be performed using a treadmill (usually the Bruce protocol; Table 5.1a, b) or cycle ergometer (Fig. 5.1). If a cycle ergometer is used, a "ramp" protocol is usually employed and has, in recent years, supplanted staged protocols. For the ramp protocol, the patient is asked to maintain a pedaling rate of ~60 pedals/minute. After pedaling against 0 resistance during an initial warm-up/equilibration period of 2–3 minutes, the pedal resistance is increased at a constant rate until the 60 pedal/minute pedaling rate can no longer be maintained. The rate at which the resistance is increased is selected based upon the patient's age, size, gender, and level of fitness, so that the patient will reach peak exercise in 8–12 minutes. As a rule of thumb, the peak work rate of normal children and adolescents tends to be ~3–4 W/kg (more for fit individuals and less for impaired individuals); the desired ramp rate can be calculated accordingly. Baseline spirometric measurements are also acquired prior to CPET (they assist in the interpretation of some of the metabolic cart data) and may be repeated postexercise [3, 8, 10].

When performing CPET studies, there are advantages and disadvantages to treadmill vs. cycle ergometry (Table 5.2). Treadmill exercise is more familiar to most patients and mimics activities of daily living better than cycle ergometry. For patients with sinus node dysfunction and rate-responsive pacemakers who are atrially paced at peak exercise, treadmill testing is preferable as it induces a more physiologic pacemaker rate response. Patients <130 cm tall often are unable to reach the pedals of a cycle ergometer. The peak oxygen consumption (and

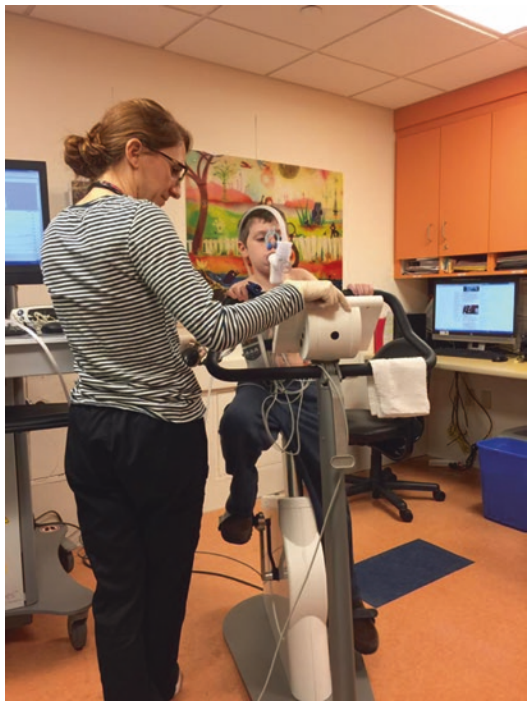


Fig. 5.1 Eight year old boy with hypoplastic left ventricle undergoing cardiopulmonary exercise test on a cycle ergometer

Table 5.1 Treadmill protocols. (**a**) Bruce protocol: multistage incremental. (**b**) Modified Bruce protocol: multistage incremental protocol used with more limited children and adults

(**a**) Bruce protocol				
Stage	Duration (min)	Speed (MPH)	Grade (%)	METS
1	3	1.7	10	5
2	3	2.5	12	7
3	3	3.4	14	10
4	3	4.2	16	13
5	3	5.0	18	15
6	3	5.5	20	18
7	3	6	22	20

(**b**) Modified Bruce protocol				
Stage	Duration (min)	Speed (MPH)	Grade (%)	METS
1	3	1.7	0	1.7
2	3	1.7	5	2.8
3	3	1.7	10	5.4
4	3	2.5	12	7.0
5	3	3.4	14	10
6	3	4.2	16	13.4
7	3	5.0	18	17.2

Table 5.2 Treadmill versus cycle ergometry

Treadmill	Cycle
Achieves slightly higher peak $\dot{V}_{O2}$ and myocardial oxygen consumption	Less interference with blood pressure determinations
Preferred for patients with sinus node dysfunction treated with rate-responsive pacemaker who are atrially paced at higher levels of exercise	Less interference with electrocardiograph
Mimics activities of daily living	Provides better estimate of external work performed
Can be used for patients <130 cm tall	Identification of ventilatory anaerobic threshold usually more straightforward
	Permits determination of $\dot{V}_{O2}$/work rate relationship
	Less risk of fall/injury

presumably, myocardial oxygen consumption) also tends to be ~5–10% higher on a treadmill. On the other hand, the greater noise and motion artifact associated with treadmill exercise is more likely to interfere with EKG analyses and blood pressure measurements. Other physiologic measurements (ventilatory anaerobic threshold and the $\dot{V}_{O2}$/work rate relationship) are more easily determined or can only be determined when a patient performs a (ramped) cycle exercise protocol. Moreover, because cycling is a non-weight-bearing activity, it is, compared to treadmill exercise, less influenced by non-cardiopulmonary factors such as body weight, orthopedic issues, etc. Consequently, the peak work rate (from a cycle ergometer) is a better index of exercise function, with a narrower range of "normal," than the endurance time on a treadmill. The peak work rate is a parameter of peak exercise function that is not directly measured by the metabolic cart. It can therefore provide a valuable "internal check" on the validity of the peak exercise data acquired by the metabolic cart. In this context, the peak work rate is far superior to the endurance time derived from the treadmill protocol. Treadmills tend to be more expensive and carry a higher risk for patient injury compared to stationary cycles. These considerations cause most pediatric exercise physiologists to prefer to use a cycle ergometer with a ramp protocol for their CPET studies [15–23]. However, high-quality CPET studies may be obtained with either equipment [3, 8, 9].

Other Protocols

To ascertain whether exercise-induced bronchoconstriction is responsible for or contributing to a patient's symptoms, postexercise spirometry may be added to a stress test with EKG monitoring or CPET. A >10% decline in the volume exhaled during the first second of a forced exhalation (FEV1) is suggestive of exercise-induced bronchospasm. Analogous declines in the average flow rate between 75% and 25% of a forced exhalation (FEF25–75) may also be observed. In normal individuals, these parameters tend to be unchanged or increase in response to exercise. Postexercise spirometry may be repeated 5, 10, 15, and 30 minutes postexercise. If evidence of bronchospasm is observed, a beta-agonist bronchodilator may be administered to determine if the bronchospasm is responsive to this therapy. An exercise protocol that causes the patient's heart rate to rise to more than 85% of that predicted within the first 2–4 minutes of exercise and remain there for ~6 minutes is thought to be more likely to provoke bronchospasm than the more gradual exercise protocols [24–26]. In pediatric patients, this may be accomplished by skipping the first two or more stages of the Bruce protocol, manually adjusting the speed and elevation of the treadmill, or manually adjusting the resistance on a cycle ergometer. When seeking a more thorough, unambiguous assessment of a patient's respiratory function during exercise, it is also often worthwhile to incorporate exercise flow-volume loop determinations into the protocol.

Depending upon the clinical or physiologic questions that are being explored, other nonstandard exercise protocols, such as steady-state exercise tests, may sometimes be employed. These protocols are generally employed in the research rather than the clinical setting. Some investigators have also used echocardiographic tables equipped with supine or semisupine cycle ergometer attachments to obtain images and perform echocardiographic measurements *during* exercise [27–29]. Others have used magnetic resonance imaging (MRI)-compatible supine cycle ergometers to permit the acquisition of immediate postexercise MRI images [30–32]. At this time, these protocols are also useful primarily in the research setting.

Table 5.3 Relative advantages and disadvantages of various exercise test protocols

Type of test	Outcome variables	Advantages	Disadvantages
6-minute walk test	Distance (m) O_2Sat BP (mm Hg)	Useful for highly impaired patients with CHF or pulmonary hypertension Validated for clinical trials Inexpensive Does not require special equipment	No effort data No EKG data Not suitable for less impaired patients
Exercise testing with electrocardiographic monitoring	Endurance time (min) O_2Sat, BP (mm Hg), EKG (HR, arrhythmias, Δ(Delta)STT)	Useful for patients with known or suspected rhythm disturbances and/or ischemic heart disease May incorporate perfusion imaging, stress echo, etc.	No effort data Provides little information regarding factors responsible for exercise intolerance
Cardiopulmonary exercise testing	Endurance time (min) or peak work rate (W, %pred), Peak V_{O2} (ml/min; %pred) O2 pulse (ml/beat, %pred) O_2Sat (%), VAT (ml/min) BP (mm Hg) EKG (HR, arrhythmias, Δ(Delta)STT) RER Peak tidal volume (ml) Peak respiratory rate Breathing reserve End-tidal pCO_2 (mm Hg) V_E/V_{CO2} slope Other outcome variables	Most appropriate for patients with CHD and other cardiopulmonary disorders Provides the most objective and quantitative assessment of exercise function Provides the most comprehensive assessment of a patient's cardiopulmonary response to exercise May incorporate perfusion imaging, stress echo, etc.	Requires more equipment and specific training

BP blood pressure, *CHF* congestive heart failure, *EKG* electrocardiograph, *HR* heart rate, *RER* respiratory exchange ratio

Patients cannot exercise as vigorously on a supine cycle ergometer compared to an upright ergometer. Consequently, the peak exercise data from these two exercise modalities are not comparable, and the clinical utility of supine cycle ergometry is limited. See Table 5.3 for a comparison of the relative advantages and disadvantages of various exercise test protocols.

References

1. Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, et al. Clinical stress testing in the pediatric age group: a statement from the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth. Circulation. 2006;113(15):1905–20.
2. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873–934.
3. Wasserman K, Hansen DA, Sue DY, Stringer WW, Sietsema KE, Sun XG, et al. Principles of exercise testing and interpretation. 5th ed. Philadelphia: Lippincott; 2012. p. 129–53.
4. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111–7.
5. Olsson LG, Swedberg K, Clark AL, Witte KK, Cleland JG. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized,

blinded intervention trials of chronic heart failure: a systematic review. Eur Heart J. 2005;26(8):778–93.
6. Gratz A, Hess J, Hager A. Peak oxygen uptake and exercise capacity: a reliable predictor of quality of life? Reply. Eur Heart J. 2009;30:1674–5.
7. Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. Am J Cardiol. 1978;41(1):69–75.
8. Takken T, Bongers BC, van Brussel M, Haapala EA, Hulzebos EHJ. Cardiopulmonary exercise testing in pediatrics. Ann Am Thorac Soc. 2017;14(Supplement_1):S123–S8.
9. Sabath RJ, White DA, K.M. T. Exercise testing protocols. In: Rowland TW, editor. Cardiopulmonary exercise testing in children and adolescents. Champaign: Human Kinetics; 2018. p. 23–39.
10. Rhodes J. Exercise testing. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. Philadelphia: Elsevier; 2006. p. 275–87.
11. Kane DA, Fulton DR, Saleeb S, Zhou J, Lock JE, Geggel RL. Needles in hay: chest pain as the presenting symptom in children with serious underlying cardiac pathology. Congenit Heart Dis. 2010;5(4):366–73.
12. Kyle WB, Macicek SL, Lindle KA, Kim JJ, Cannon BC. Limited utility of exercise stress tests in the evaluation of children with chest pain. Congenit Heart Dis. 2012;7(5):455–9.
13. Kane DA, Friedman KG, Fulton DR, Geggel RL, Saleeb SF. Needles in Hay II: detecting cardiac pathology by the pediatric chest pain standardized clinical assessment and management plan. Congenit Heart Dis. 2016;11(5):396–402.
14. Friedman KG, Kane DA, Rathod RH, Renaud A, Farias M, Geggel R, et al. Management of pediatric chest pain using a standardized assessment and management plan. Pediatrics. 2011;128(2):239–45.
15. Anderson PA, Sleeper LA, Mahony L, Colan SD, Atz AM, Breitbart RE, et al. Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network multicenter study. J Am Coll Cardiol. 2008;52(2):85–98.
16. Atz AM, Zak V, Mahony L, Uzark K, D'Agincourt N, Goldberg DJ, et al. Longitudinal outcomes of patients with single ventricle after the Fontan procedure. J Am Coll Cardiol. 2017;69(22):2735–44.
17. Sleeper LA, Anderson P, Hsu DT, Mahony L, McCrindle BW, Roth SJ, et al. Design of a large cross-sectional study to facilitate future clinical trials in children with the Fontan palliation. Am Heart J. 2006;152(3):427–33.
18. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li J, et al. A cross-sectional study of exercise performance during the first two decades of life following the Fontan operation. J Am Coll Cardiol. 2008;52:99–107.
19. Karamlou T, Poynter JA, Walters HL 3rd, Rhodes J, Bondarenko I, Pasquali SK, et al. Long-term functional health status and exercise test variables for patients with pulmonary atresia with intact ventricular septum: a Congenital Heart Surgeons Society study. J Thorac Cardiovasc Surg. 2013;145(4):1018–25; discussion 25-7
20. Meadows J, Lang P, Marx 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(2):108–13.
21. Rhodes J, Curran TJ, Camil L, Rabideau NC, Fulton DR, Gauthier NS, et al. Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. Pediatrics. 2005;116:1339–45.
22. Rhodes J, Dave A, Pulling MC, Geggel RL, Marx GR, Fulton DR, et al. Effect of pulmonary artery stenoses on the cardiopulmonary response to exercise following repair of tetralogy of Fallot. Am J Cardiol. 1998;81(10):1217–9.
23. Sutton NJ, Peng L, Lock JE, Lang P, Marx GR, Curran TJ, et al. Effect of pulmonary artery angioplasty on exercise function after repair of tetralogy of Fallot. Am Heart J. 2008;155(1):182–6.
24. van Leeuwen JC, Driessen JM, Kersten ET, Thio BJ. Assessment of exercise-induced bronchoconstriction in adolescents and young children. Immunol Allergy Clin N Am. 2013;33(3):381–94, viii–ix
25. MacCallum DS, Comeau D. Exercise-induced bronchoconstriction. Curr Sports Med Rep. 2016;15(3):128–9.
26. Pasnick SD, Carlos WG 3rd, Arunachalam A, Celestin FM, Parsons JP, Hallstrand TS, et al. Exercise-induced bronchoconstriction. Ann Am Thorac Soc. 2014;11(10):1651–2.
27. Goebel B, Arnold R, Koletzki E, Ulmer HE, Eichhorn J, Borggrefe M, et al. Exercise tissue Doppler echocardiography with strain rate imaging in healthy young individuals: feasibility, normal values and reproducibility. Int J Cardiovasc Imaging. 2007;23(2):149–55.
28. Poerner TC, Goebel B, Figulla HR, Ulmer HE, Gorenflo M, Borggrefe M, et al. Diastolic biventricular impairment at long-term follow-up after atrial switch operation for complete transposition of the great arteries: an exercise tissue Doppler echocardiography study. J Am Soc Echocardiogr. 2007;20(11):1285–93.
29. Harada K, Toyono M, Yamamoto F. Assessment of right ventricular function during exercise with quantitative Doppler tissue imaging in children late after repair of tetralogy of Fallot. J Am Soc Echocardiogr. 2004;17(8):863–9.
30. Roest AA, Lamb HJ, van der Wall EE, Vliegen HW, van den Aardweg JG, Kunz P, et al. Cardiovascular response to physical exercise in adult patients after atrial correction for transposition of the great arteries assessed with magnetic resonance imaging. Heart. 2004;90(6):678–84.
31. Roest AAW, Helbing WA, Kunz P, van den Aardweg JG, Lamb HJ, Vliegen HW, et al. Exercise MR imaging in the assessment of pulmonary regurgitation and biventricular function in patients after tetralogy of Fallot repair. Radiology. 2002;223:204–11.
32. Vliegen HW, van Straten A, de Roos A, Roest AAW, Schoof PH, Zwinderman AH, et al. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacemnt in adults late after repair of tetralogy of Fallot. Circulation. 2002;106:1703–7.

Exercise Stress Echocardiography

6

Iqbal El-Assaad, Keri M. Shafer, and Ming Hui Chen

Background

Exercise stress echocardiography (ESE) is a versatile diagnostic tool that has been integrated into the standard clinical assessment of adult patients with coronary artery disease, hypertrophic cardiomyopathy (HCM), and pulmonary hypertension [1–7]. Experience with ESE in children with these disorders is more limited. Given the potential value of this technology in pediatrics is significant, its role in the clinical management of pediatric patients continues to grow and evolve [8–12]. Since 2006, Boston Children's Hospital has been performing stress echocardiography for both ischemia and assessment of hemodynamics of exercise [10–12] (Fig. 6.1).

ESE can be performed with the use of treadmill exercise or upright, supine, or semisupine cycle ergometer. Treadmill exercise has the advantage of more closely resembling daily physical activities than cycle ergometer, and treadmill exercise test has been shown to be associated with higher peak $\dot{V}_{O2}$. Other physiologic measurements are easier to obtain with upright cycle ergometry. Motion artifact and interference from lung tissues render the acquisition of imaging data *during* treadmill, and even upright cycle ergometry, difficult or impossible. Imaging data (including Doppler and strain imaging) during exercise can be incorporated into supine or semisupine cycle ergometry protocols [9], but the metabolic data obtained from these modalities are generally lower. Optimally, an exercise laboratory performing stress echocardiography would have a full complement of exercise modalities to allow tailoring to staff and patient preferences and the clinical questions posed; practical considerations may limit labs to treadmill or cycle ergometry.

I. El-Assaad
Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Department of Pediatrics, Harvard Medical School, Boston, MA, USA
e-mail: Iqbal.El-Assaad@cardio.chboston.org

K. M. Shafer
Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
e-mail: Keri.Shafer@cardio.chboston.org

M. H. Chen (✉)
Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA
e-mail: minghui.chen@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_6

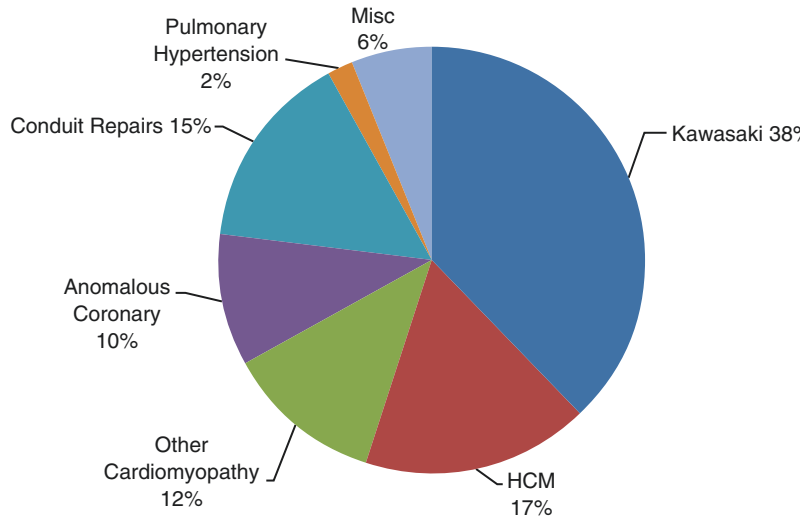


Fig. 6.1 Exercise stress echos at Boston Children's Hospital from 2006 to 2018 ($n > 1300$). Misc miscellaneous, HCM hypertrophic cardiomyopathy

Assessment of Myocardial Ischemia

Ischemia occurs when myocardial oxygen demand exceeds myocardial oxygen supply. The basis of exercise stress testing lies in using exercise to increase myocardial oxygen demand. Onset of wall motion abnormalities and regional wall motion abnormalities on echocardiography precede the onset of electrocardiographic (EKG) changes or symptoms on the ischemic cascade; therefore, stress echo offers an opportunity to diagnose ischemia prior to clinical presentation [8]. To systematically assess regional wall motion, the American Society of Echocardiography recommends the use of a 16- or 17-segment model [13]. Regional wall motion of all the left ventricular segments should be graded by visual inspection both at rest and post-exercise as normal/hyperdynamic, hypokinetic, akinetic, or dyskinetic/aneurysmal. In addition to identifying wall motion abnormalities, it is important to distinguish between hypokinesis/akinesis and dyssynchrony. Dyssynchrony has many different etiologies (ventricular pacing, bundle branch blocks) and can complicate the accurate assessment of ischemia in these regions. The schema used for the interpretation of ischemia for stress echocardiography is shown in Table 6.1. This is consistent with the American Society of Echocardiography guidelines [13].

In addition to the evaluation of segmental function pre- and post-exercise, the global left ventricular (LV) response to stress should be assessed [13]. In normal individuals, LV volumes immediately post-exercise should be smaller than those present at rest, and LV function (ejection fraction) should be higher. These changes develop as a consequence of the increased contractility and decreased systemic vascular resistance that accompanies exercise, as well as the abrupt decline in preload that accompanies the loss of the skeletal muscles' pumping action when exercise is terminated (see Chap. 3).

At Boston Children's Hospital, to fully assess all regions of the myocardium in children, baseline and immediate post-exercise images are obtained: apical four-chamber, three-chamber (i.e., apical long axis), and two-chamber views; parasternal long-axis and short-axis views (base, mid-papillary, and apex)

Table 6.1 Schematic used to assess for ischemia

Pre-exercise	Post-exercise	→	Ischemia
Normal	Normal or hyperkinetic	→	No
Normal	Hypokinetic, akinetic, or dyskinetic	→	Yes
Hypokinetic	Normal	→	No
Hypokinetic	Akinetic or dyskinetic	→	Yes
Akinetic/dyskinetic	Akinetic or dyskinetic	→	No, infarcted[a]

Modified from Chen et al., and also ASE [10, 13]
[a]In patients with a ventricular septal patch, wall motion in that segment may be akinetic/dyskinetic without infarction or ischemia

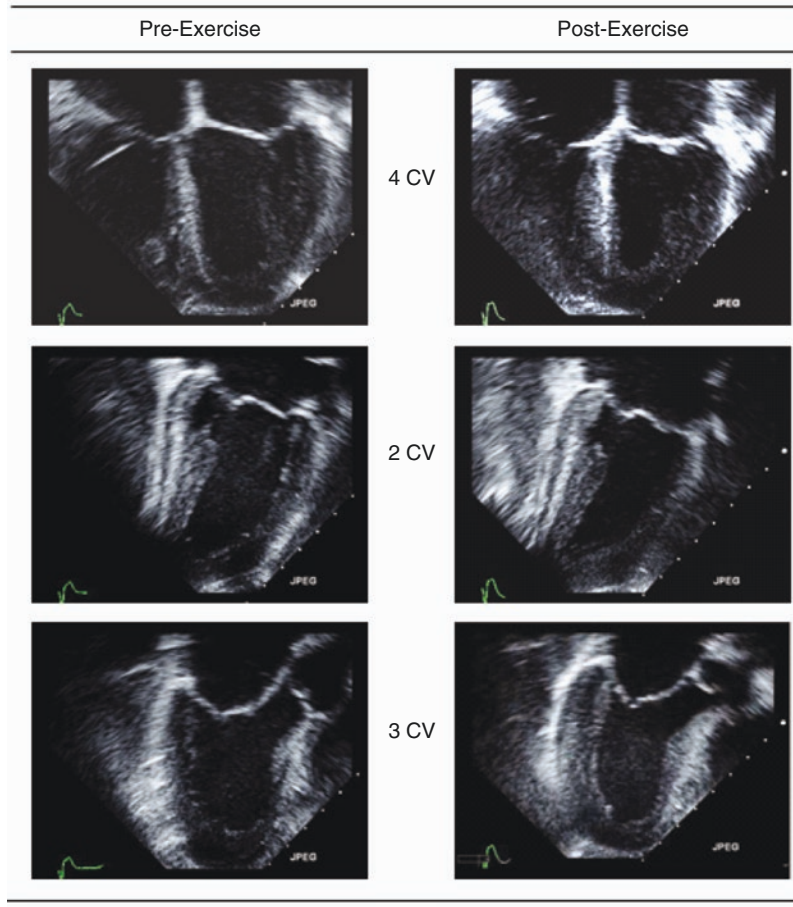


Fig. 6.2 Pre- and post-exercise apical four-chamber, two-chamber, and three-chamber long-axis views. Abbreviation: CV = chamber view. (Reprinted with permission from [10])

(Figs. 6.2 and 6.3) [10]. When acquiring pre-exercise images, it is important to identify the best imaging windows to utilize post-exercise. It is also important to ensure that EKG lead placement allows for adequate acoustic windows for imaging. Post-exercise images should be obtained promptly (within 90 seconds), before a significant drop in heart rate and change in hemodynamics have occurred. Given the importance of rapid imaging, sonographer training and experience with ESE is needed to obtain an optimal study [10].

In patients with congenital heart disease, the presence of a ventricular septal defect (VSD) patch left bundle branch block, paced rhythms, right ventricular (RV) pressure or volume overload, etc. may result in wall motion abnormalities unrelated to myocardial ischemia and should be accounted for during the interpretation of stress echocardiographic studies.

Assessment of Patients with Known or Suspected Hypertrophic Cardiomyopathy

For patients with diagnosed or suspected HCM, the purpose of ESE is usually to accurately identify and estimate left ventricular outflow tract (LVOT) gradients, characterize systolic anterior motion (SAM) of the mitral valve, and assess mitral valve function. In these cases, standardized two-dimensional and Doppler images are obtained at rest and immediately post-exercise. Table 6.2 illustrates the clinical protocol for HCM utilized by Boston Children's Hospital. At least two beat clips with 2D and three beat clips for Doppler measurements are obtained. Pre-exercise, images are acquired from apical and parasternal views with special attention to the LVOT and the left ventricle.

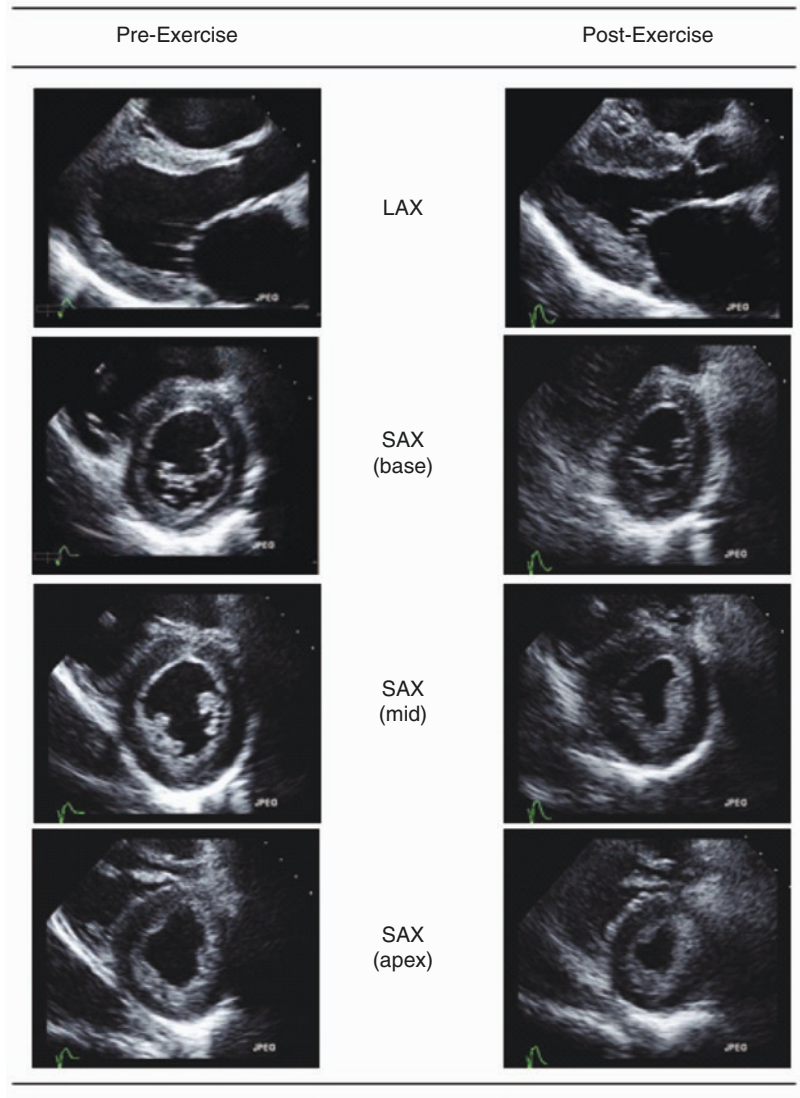


Fig. 6.3 Pre- and post-exercise parasternal long-axis view (LAX) and short-axis (SAX) views at the base, mid-ventricle, and apex. (Reprinted with permission from [10])

The degree of mitral regurgitation (MR) and the presence of systolic anterior motion (SAM) of the mitral valve are also assessed. Post-exercise, priority should be given to the LVOT images and gradients and mitral valve assessment (Table 6.2).

A common difficulty in the ESE evaluation of patients with HCM is differentiating the mitral regurgitation from the LVOT jet, since both jets are located in proximity to each other and occur during systole. Careful analysis of the waveform of the continuous wave Doppler signal can help distinguish between the MR and LVOT obstructions (Fig. 6.4). The Doppler of LVOT obstruction characteristically has a gradual increase in early systole with midsystolic acceleration and a late peak ("dagger-shaped" signal). In contrast, the mitral regurgitation continuous wave Doppler signal begins at the onset of systole and rapidly attains markedly increased velocity (usually >5 m/s), which then persists throughout systole ("bell-shaped" signal) [3]. The mitral regurgitation velocity (which reflects the pressure gradients between the LV systolic pressure minus the left atrial pressure) is higher than the LVOT velocity usually (Fig. 6.4).

Table 6.2 Boston Children's Hospital ESE protocol for the assessment of left ventricular outflow tract (LVOT) gradients in patients with hypertrophic cardiomyopathy (HCM)

Pre-exercise	Post-exercise
Apical views *Four-chamber view (2D/Doppler)* Degree of mitral regurgitation Presence of SAM Measure MR velocity RVSP LV walls and regional function *Five-chamber view* Measure the LVOT gradient; pulse from mid-cavity toward the LVOT (use CW if gradient is present) *Three-chamber view* Check degree of mitral regurgitation CW of the MR (if available) LVOT velocity/gradient and location Regional wall motion assessment	*Apical views* Assess peak LVOT gradient and determine the location (make sure to separate from MR jet) Assess the MR severity by color Obtain MR velocity by CW (apical or parasternal) Assess the presence of SAM from apical and parasternal views Assess RVSP
Parasternal long-axis (LAX) view Check mitral valve structure and function Check degree of MR RVSP—if not available from apical views	*Parasternal long-axis (LAX) view* Check degree of MR RVSP—if not available from apical views
Parasternal short-axis (SAX) view Assess LV function and wall motion in 17 segments Short-axis views of the base, mid-ventricle, and apex	*Parasternal short-axis (SAX) view* Assess LV function and wall motion in 17 segments Short-axis views of the base, mid-ventricle, and apex

SAM systolic anterior motion, *MR* mitral regurgitation, *RVSP* right ventricular systolic pressure, *CW* continuous wave Doppler

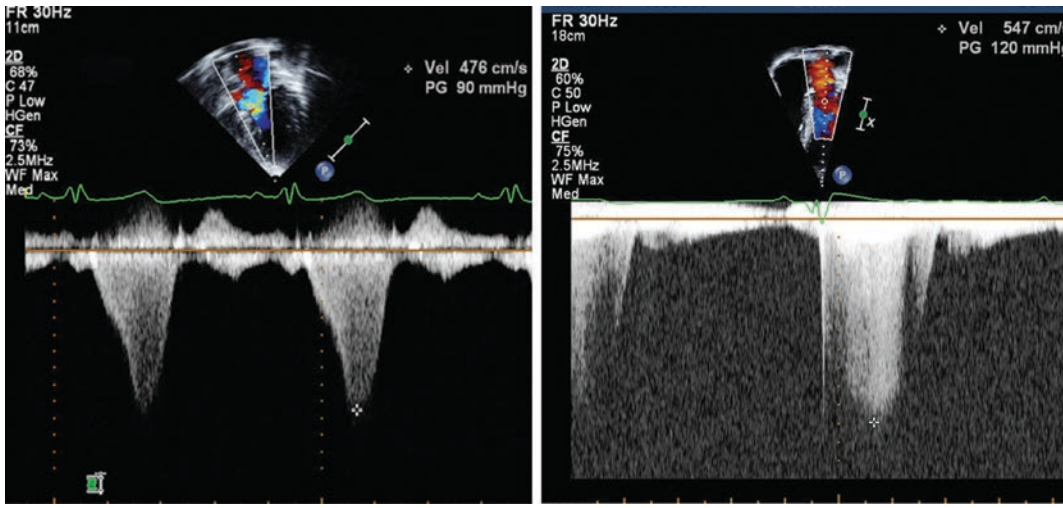


Fig. 6.4 Continuous wave Doppler recordings of the left ventricular outflow tract (LVOT) (left panel) from a 12-year-old girl with hypertrophic cardiomyopathy with LVOT gradient with exercise. Peak gradient is 90 mm Hg. The LVOT tracing has a "dagger shape" with the initial jet velocity increase being more gradual and peaking later in systole. For comparison, a typical continuous wave Doppler recording of the mitral valve is shown on the right panel. Note that the mitral regurgitation jet begins at the onset of systole and attains a peak gradient more rapidly

Acquisition of images and tracings from the apical four-chamber, two-chamber, and three-chamber views may be necessary to adequately distinguish the two systolic jets. In some normal, young subjects who are athletes, LVOT gradients as high as 50 mm Hg may be detected immediately post-exercise. These gradients develop due to the increase in LV contractility and the dramatic decline in systemic vascular resistance that occurs during exercise, coupled with the abrupt decline in left ventricular preload that occurs when exercise is terminated and the pumping action of the skeletal muscles is suddenly eliminated [14]. (See Chap. 3.)

Assessment of Patients with Known or Suspected Pulmonary Hypertension

For patients with diagnosed or suspected pulmonary hypertension, the tricuspid regurgitation jet velocity should be measured at rest and also with exercise. This is usually undertaken from the apical four-chamber view, although parasternal views may also be used, depending on the echocardiographic windows. To support the findings from Doppler echocardiography, the ventricular septal configuration should also be assessed from the parasternal short-axis view pre- and post-exercise. Although some laboratories acquire Doppler tracings with patients pedaling on a semisupine or an upright cycle ergometer, we have acquired good tracings immediately post-exercise with the patient lying on his/her left side. Studies have found that high-quality Doppler tracings correlate fairly well with invasive measurements. Low-quality Doppler tracings, however, correlate poorly with invasive measurements [7]. When assessing RV pressure estimates, it is also important to recognize that some patients may develop a significant flow-related right ventricular outflow tract gradient during exercise; this phenomenon must be taken into account when assessing tricuspid regurgitation jet velocity data [7, 15]. While clearly feasible, ESE is currently used only for the subgroups of pulmonary artery hypertension patients, with the majority of patients still being evaluated with the use of 6-minute walk tests.

Conclusions

1. Exercise stress echocardiography is feasible in the pediatric and congenital heart population.
2. While supine cycle ergometry may offer advantages for acquiring image data during exercise, standard exercise techniques permit reasonable stress imaging pre- and immediate post-exercise.
3. The precise role of exercise stress echocardiography in pediatrics and congenital heart disease is clearly evolving.

References

1. Drinko JK, Nash PJ, Lever HM, Asher CR. Safety of stress testing in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2004;93(11):1443–4, A1412
2. Olivotto I, Montereggi A, Mazzuoli F, Cecchi F. Clinical utility and safety of exercise testing in patients with hypertrophic cardiomyopathy. G Ital Cardiol. 1999;29(1):11–9.
3. Rowin EJ, Maron BJ, Olivotto I, Maron MS. Role of exercise testing in hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2017;10(11):1374–86.
4. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2011;142(6):e153–203.
5. Rudski LG, Gargani L, Armstrong WF, Lancellotti P, Lester SJ, Grunig E, et al. Stressing the cardiopulmonary vascular system: the role of echocardiography. J Am Soc Echocardiogr. 2018;31(5):527–550 e511.
6. Mangla A, Oliveros E, Williams KA Sr, Kalra DK. Cardiac imaging in the diagnosis of coronary artery disease. Curr Probl Cardiol. 2017;42(10):316–66.
7. van Riel AC, Opotowsky AR, Santos M, Rivero JM, Dhimitri A, Mulder BJ, et al. Accuracy of echocardiography to estimate pulmonary artery pressures with exercise: a simultaneous invasive-noninvasive comparison. Circ Cardiovasc Imaging. 2017;10(4):pii: e005711.
8. Thompson WR. Stress echocardiography in paediatrics: implications for the evaluation of anomalous aortic origin of the coronary arteries. Cardiol Young. 2015;25(8):1524–30.

9. Cifra B, Dragulescu A, Border WL, Mertens L. Stress echocardiography in paediatric cardiology. Eur Heart J Cardiovasc Imaging. 2015;16(10):1051–9.
10. Chen MH, Abernathey E, Lunze F, Colan SD, O'Neill S, Bergersen L, et al. Utility of exercise stress echocardiography in pediatric cardiac transplant recipients: a single-center experience. J Heart Lung Transplant. 2012;31(5):517–23.
11. Hasan BS, Lunze FL, McElhinney DB, Stantcheva E, Brown DW, Rhodes J, Chen MH. Exercise stress echocardiographic assessment of outflow tract and ventricular function in patients with an obstructed right ventricular-to-pulmonary artery conduit after repair of conotruncal heart defects. Am J Cardiol. 2012;110(10):1527–33.
12. Hasan BS, Lunze FL, Chen MH, Brown DW, Boudreau MJ, Rhodes J, McElhinney DB. Effects of transcatheter pulmonary valve replacement on the hemodynamic and ventricular response to exercise in patients with obstructed right ventricle-to-pulmonary artery conduits. JACC Cardiovasc Interv. 2014;7(5):530–42.
13. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG. American society of echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr. 2007;20(9):1021–41.
14. Wittlieb-Weber CA, Cohen MS, McBride MG, Paridon SM, Morrow R, Wasserman M, et al. Elevated left ventricular outflow tract velocities on exercise stress echocardiography may be a normal physiologic response in healthy youth. J Am Soc Echocardiogr. 2013;26(12):1372–8.
15. Wright SP, Opotowsky AR, Buchan TA, Esfandiari S, Granton JT, Goodman JM, et al. Flow-related right ventricular – pulmonary arterial pressure gradients during exercise. Cardiovasc Res. 2019;115(1):222–9.

7 Other Modalities: Assessment of Pulmonary Response and Measurement of Cardiac Output

Alexander R. Opotowsky and Jonathan Rhodes

In certain clinical and/or research settings, it is helpful to incorporate additional technologies/modalities into the standard cardiopulmonary exercise test (CPET). Some of these will now be discussed.

Exercise Flow-Volume Loops

Exercise flow-volume loops (FVL) can provide insights into the pulmonary limitations to exercise. Software packages are available for most modern metabolic carts which permit the acquisition of the data required for these analyses. The protocol for exercise FVL requires the patient to perform several pre-exercise maximal expiratory and inspiratory maneuvers between the patient's total lung capacity (TLC) and residual volume (RV). The effort with the largest FVL is used to define the reference maximal FVL. The patient is then instructed to take a maximal inspiration and then exhale and breathe normally. This maneuver permits one to place the patient's tidal FVL within the reference maximal FVL. This maneuver can then be repeated at any time during an exercise test, and the relationship between the patient's tidal FVL during exercise and the baseline maximal FVL can be assessed (Fig. 7.1) [1]. Useful parameters to assess are: the degree of expiratory flow limitation, the end-expiratory lung volume (EELV), and the end-inspiratory lung volume (EILV) [1].

Expiratory flow limitation can be quantitated by calculating the percentage of the exercise tidal volume FVL that meets or exceeds the expiratory boundary of the baseline maximal FVL. In normal individuals, expiratory airflow limitation is present over only ~25% of the tidal volume at peak exercise workloads and generally occurs only at lower lung volumes, near EELV. In patients with obstructive lung disease, however, flow limitation is observed

A. R. Opotowsky (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Exercise Physiology Laboratory, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: alexander.opotowsky@cardio.chboston.org

J. Rhodes
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_7

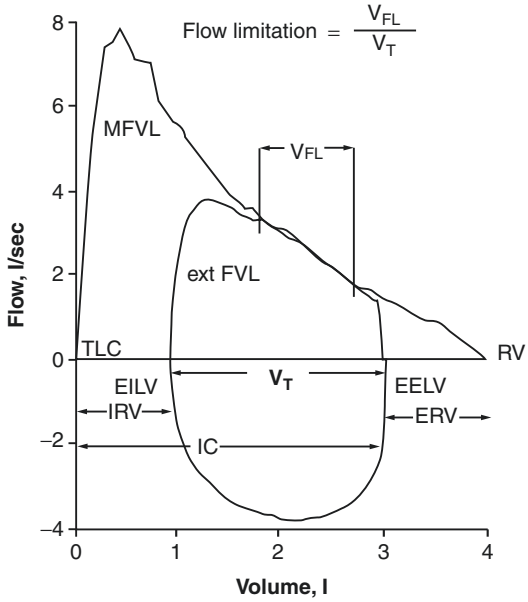


Fig. 7.1 Defining expiratory flow limitation. Tidal exercise flow volume loops (ext FVLs) are aligned within the maximal flow volume envelope (MFVL) according to a measured end-expiratory lung volume (EELV). The percent of the tidal breath (VFL) that expiratory air flows meet or exceed the maximal expiratory flows (MEFs) is used as an estimate as to the degree of expiratory flow limitation. EILV end-inspiratory lung volume; ERV expiratory reserve volume; IC inspiratory capacity; IRV inspiratory reserve volume; RV reserve volume; TLC total lung capacity; VT tidal volume. (Reprinted with permission from [1])

across a large portion of the tidal volume, even at relatively low exercise intensities [2–4]. Flow limitation across a high percentage of the exercise FVL also may be observed in athletes and other extremely fit individuals. However, this phenomenon is only observed at high exercise intensities and is due to the high metabolic rate and high levels of ventilation that these individuals can achieve during exercise [5].

In normal individuals, EELV tends to fall during exercise. At rest, expiration is usually a passive phenomenon due primarily to the elastic recoil of the chest wall after inspiration. During exercise, muscles are recruited to augment expiration, lower the EELV, and help increase tidal volume. In addition, the elastic and gravitational energies that accumulate in the rib cage, abdomen, and diaphragm as a consequence of active expiration provide passive recoil at the initiation of the subsequent inspiration and help to augment the next breath. Patients with obstructive lung disease, however, develop air trapping during exercise. This phenomenon is manifested by an increase in EELV during exercise [1, 6]. To compensate for their elevated EELV and to maintain their tidal volume, patients with obstructive lung disease may also increase their EILV by recruiting their muscles of inspiration. Although normal subjects may increase their EILV to almost 90% of total lung capacity during intense exercise, patients with obstructive lung disease and air trapping may develop elevated EILV values even at low exercise intensities. As EILV approaches total lung capacity, lung compliance begins to fall, and thus the inspiratory elastic load increases [7]. This results in an energetically unfavorable breathing pattern that places increased strain on the muscles of inspiration (i.e., it requires more energy to move the chest wall at high lung volumes), which may in turn contribute to a patient's exercise limitation [1–3].

Patients with restrictive lung disease have a low EELV and will have an EILV that approaches their inspiratory capacity, even at low exercise intensities. These abnormalities are a reflection of their abnormally small lung volumes. Once again, similar phenomena may be observed in highly fit individuals, but only at high exercise intensities, and is a consequence of the high metabolic rates and minute ventilations that these individuals can achieve [2].

The acquisition of exercise FVLs does not significantly interfere with other CPET measurements [8]. Moreover, patients with congenital heart disease commonly have a combination of ventilatory issues that may affect their cardiopulmonary response to exercise [9–13]. The more detailed and unambiguous assessments of pulmonary function during exercise that are provided by exercise FVL technology can be of unique value to clinicians for these physiologically complex patients. However, experience in the pediatric and congenital heart disease population is quite limited and the role of this technology is yet to be defined.

Measurement of Cardiac Output

Oxygen consumption (V_{O2}) is a function of cardiac output (CO) as well as hemoglobin concentration, arterial oxygen saturation (and to a small

extent dissolved oxygen), and mixed venous oxygen saturation. Therefore, measurement of oxygen consumption does not provide a *direct* assessment of the cardiac response to the demands of exercise (i.e., augmentation of CO). Measurement of CO can be performed during exercise, either noninvasively or invasively.

Noninvasive Measurement of Cardiac Output: Inert Gas Rebreathing

Various noninvasive methods can be used to estimate CO including echocardiography, bioimpedance, pulse wave assessment, carbon dioxide rebreathing, and inert gas rebreathing. Inert gas rebreathing appears to be the most reliable currently available method and can be applied both at rest and during exercise.

Pulmonary blood flow (PBF) can be measured using an inert gas rebreathing method. This involves rebreathing a known volume and concentration of two inert gases. One of the gases is blood-soluble and absorbed into the blood in proportion to PBF. The other gas is blood-insoluble and is used to measure the combined volume of the lungs, airways, tubing, valve, and rebreathing bag. The approach was described many decades ago, [14] but was cumbersome to perform until the more recent introduction of more user-friendly automated technology.

Gas rebreathing measurements of CO appear to be acceptably accurate, with clinically reasonable correlation and agreement with other clinical methods of CO estimation such as thermodilution, true Fick, and cardiac magnetic resonance. Studies support the applicability of this technique at rest in children, [15] patients with congenital heart disease or pulmonary hypertension, [16, 17] and also during mechanical ventilation, [18] or during exercise [19, 20].

There are specific situations where gas rebreathing CO may be inaccurate, however. This approach estimates PBF and not systemic CO (i.e., Qp rather than Qs); so, in the presence of right-to-left shunting, PBF (and consequently the rebreathing CO estimate) will be less than systemic CO. Gas rebreathing is also inaccurate in the presence of left-to-right shunting because of early recirculation of the soluble gas through the lungs.

Invasive Measurements of Cardiac Output

CO can be measured during exercise via catheterization, either with sampling of mixed venous blood (usually from the pulmonary artery) and using the Fick equation or with a dilution method, usually thermodilution [21]. Estimated or "assumed $\dot{V}_{O2}$ Fick" uses a gross estimate of oxygen consumption based upon a nomogram, while "true Fick" employs a simultaneous, direct measurement of $\dot{V}_{O2}$. At rest, nomograms can estimate resting $\dot{V}_{O2}$ with moderate accuracy, but this methodology cannot be used to estimate $\dot{V}_{O2}$ during exercise. Consequently, "assumed $\dot{V}_{O2}$ Fick" cannot be applied to the estimation of CO during exercise. Both "true Fick," with direct measurement of $\dot{V}_{O2}$, and thermodilution are accurate during exercise, however. The details and pitfalls of these techniques are beyond the scope of this chapter and require experience and understanding of key assumptions. For example, these measurements can be challenging or impossible in some patients with congenital heart disease. The presence of shunting precludes thermodilution-based measurements and requires more thoughtful interpretation of Fick-based measurements. Further, some patients with congenital heart disease may not have a chamber or other anatomic site where systemic venous blood is fully mixed. For example, in patients with a total cavopulmonary anastomosis, preferential streaming of inferior vena cava (IVC) blood toward one lung and superior vena cava (SVC) blood to the other is often present, while coronary sinus blood drains into the pulmonary venous atrium. This physiology precludes the estimation of CO using dilution techniques.

Blood Sampling During Exercise

In some cases, it is helpful to obtain an arterial blood gas during exercise, primarily for a reliable, direct measurement of arterial pCO_2

(currently available noninvasive, transcutaneous pCO_2 monitors are too inaccurate and/or respond too slowly to be of value for estimating arterial pCO_2 during a progressive exercise test). For some metabolic defects, endocrinological disorders, and other conditions, blood sampling for glucose, lactate, cortisol, growth hormone, and other variables may be incorporated into an exercise test, when indicated, for clinical or research purposes.

Exercise Oscillatory Ventilation

Many CPET measurements focus on a single value at a specific time point (e.g., peak $\dot{V}_{O2}$). There is additional information to be gained from the patterns of response that may or may not be readily quantified. For example, a drop in $\dot{V}_{O2}$ toward the peak of exercise provides specific information not necessarily captured by a single value. Another instance of dynamic response is exercise oscillatory ventilation (EOV). This term refers to a pattern of periodic breathing with oscillating minute ventilation, rather than a steady nonlinear increase, with exercise. EOV is comparable to Cheyne–Stokes respiration—a periodic breathing pattern sometimes observed in patients with severe heart failure [22]. However, EOV is more common and can be present in patients without decompensated heart failure.

Several studies in acquired heart failure have reported that the presence of EOV is predictive of adverse events (e.g., mortality, arrhythmia) independent of peak $\dot{V}_{O2}$ or the $\dot{V}_E/\dot{V}_{CO2}$ slope [23, 24]. There has been less research among patients with CHD. One study reported that EOV was present in 37.5% of 253 patients with a Fontan circulation and that its presence was associated with an increased risk for death or transplantation or nonelective cardiovascular hospitalization [25].

Unfortunately, there is no universally accepted definition of EOV, and the determination of the presence or absence of EOV can be more challenging than one might expect. We use the following definition: regular oscillations with amplitude >15% of average $\dot{V}_E$ during the exercise test, present for >60% of total exercise duration. Some definitions require a quantitative measure of regularity (e.g., cycle length with coefficient of variation <20%) and the duration of the cycles (e.g., 40–140 seconds) [24]. EOV may exist across a spectrum of severity, and quantitative assessment of the duration of the oscillatory period, amplitude, and timing during exercise (e.g., early versus late) may provide more information, but this remains speculative.

References

1. Johnson BD, Weisman IM, Zeballos RJ, Beck KC. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. Chest. 1999;116(2):488–503.
2. Dueck R. Assessment and monitoring of flow limitation and other parameters from flow/volume loops. J Clin Monit Comput. 2000;16(5–6):425–32.
3. Younes M. Load responses, dyspnea, and respiratory failure. Chest. 1990;97(3 Suppl):59S–68S.
4. Johnson BD, Scanlon PD, Beck KC. Regulation of ventilatory capacity during exercise in asthmatics. J Appl Physiol (1985). 1995;79(3):892–901.
5. Johnson BD, Saupe KW, Dempsey JA. Mechanical constraints on exercise hyperpnea in endurance athletes. J Appl Physiol (1985). 1992;73(3):874–86.
6. Levine S, Gillen M, Weiser P, Feiss G, Goldman M, Henson D. Inspiratory pressure generation: comparison of subjects with COPD and age-matched normals. J Appl Physiol (1985). 1988;65(2):888–99.
7. Younes M, Kivinen G. Respiratory mechanics and breathing pattern during and following maximal exercise. J Appl Physiol Respir Environ Exerc Physiol. 1984;57(6):1773–82.
8. Bussotti M, Agostoni P, Durigato A, Santoriello C, Farina S, Brusasco V, et al. Do maximum flow-volume loops collected during maximum exercise test alter the main cardiopulmonary parameters? Chest. 2009;135(2):425–33.
9. Opotowsky AR, Landzberg MJ, Earing MG, Wu FM, Triedman JK, Casey A, et al. Abnormal spirometry after the Fontan procedure is common and associated with impaired aerobic capacity. Am J Physiol Heart Circ Physiol. 2014;307(1):H110–7.
10. Ginde S, Bartz PJ, Hill GD, Danduran MJ, Biller J, Sowinski J, et al. Restrictive lung disease is an independent predictor of exercise intolerance in the adult with congenital heart disease. Congenit Heart Dis. 2013;8(3):246–54.
11. Hawkins SM, Taylor AL, Sillau SH, Mitchell MB, Rausch CM. Restrictive lung function in pediatric patients with structural congenital heart disease. J Thorac Cardiovasc Surg. 2014;148(1):207–11.

12. Sterrett LE, Ebenroth ES, Query C, Ho J, Montgomery GS, Hurwitz RA, et al. Why exercise capacity does not improve after pulmonary valve replacement. Pediatr Cardiol. 2014;35(8):1395–402.
13. Sterrett LE, Ebenroth ES, Montgomery GS, Schamberger MS, Hurwitz RA. Pulmonary limitation to exercise after repair of d-transposition of the great vessels: atrial baffle versus arterial switch. Pediatr Cardiol. 2011;32(7):910–6.
14. Sackner MA, Greeneltch D, Heiman MS, Epstein S, Atkins N. Diffusing capacity, membrane diffusing capacity, capillary blood volume, pulmonary tissue volume, and cardiac output measured by a rebreathing technique. Am Rev Respir Dis. 1975;111(2):157–65.
15. Wiegand G, Kerst G, Baden W, Hofbeck M. Noninvasive cardiac output determination for children by the inert gas-rebreathing method. Pediatr Cardiol. 2010;31(8):1214–8.
16. Marma AK, Opotowsky AR, Fromm BS, Ubeda-Tikkanen A, Porras D, Rhodes J. Noninvasive cardiac output estimation by inert gas rebreathing in pediatric and congenital heart disease. Am Heart J. 2016;174:80–8.
17. Hoeper MM, Maier R, Tongers J, Niedermeyer J, Hohlfeld JM, Hamm M, et al. Determination of cardiac output by the fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. Am J Respir Crit Care Med. 1999;160(2):535–41.
18. Perak AM, Opotowsky AR, Walsh BK, Esch JJ, DiNardo JA, Kussman BD, et al. Noninvasive cardiac output estimation by inert gas rebreathing in mechanically ventilated pediatric patients. J Pediatr. 2016;177:184–190 e183.
19. Agostoni P, Cattadori G, Apostolo A, Contini M, Palermo P, Marenzi G, et al. Noninvasive measurement of cardiac output during exercise by inert gas rebreathing technique: a new tool for heart failure evaluation. J Am Coll Cardiol. 2005;46(9):1779–81.
20. Fontana P, Boutellier U, Toigo M. Non-invasive haemodynamic assessments using innocor during standard graded exercise tests. Eur J Appl Physiol. 2010;108(3):573–80.
21. Guyton AC, Jones CE, Coleman TG. Cardiac output and its regulation. 2d ed. Philadelphia: Saunders; 1973.
22. Piepoli MF, Ponikowski PP, Volterrani M, Francis D, Coats AJ. Aetiology and pathophysiological implications of oscillatory ventilation at rest and during exercise in chronic heart failure. Do Cheyne and stokes have an important message for modern-day patients with heart failure? Eur Heart J. 1999;20(13):946–53.
23. Corra U, Giordano A, Bosimini E, Mezzani A, Piepoli M, Coats AJ, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. Chest. 2002;121(5):1572–80.
24. Dhakal BP, Murphy RM, Lewis GD. Exercise oscillatory ventilation in heart failure. Trends Cardiovasc Med. 2012;22(7):185–91.
25. Nathan AS, Loukas B, Moko L, Wu F, Rhodes J, Rathod RH, et al. Exercise oscillatory ventilation in patients with fontan physiology. Circ Heart Fail. 2015;8(2):304–11.

8 Supervision and Safety Precautions for Exercise Testing

Tracy J. Curran

Exercise testing is an extremely low-risk undertaking for children and patients with congenital heart disease [1–4]. The use of this testing modality has become increasingly common in recent years and has grown to include the testing of patients previously considered by some to be at high risk. Indeed, the American Heart Association consensus statement recently concluded that the only absolute contraindications to exercise testing are acute myocardial or pericardial inflammatory disease or patients with severe outflow obstruction in whom surgical intervention is clearly indicated [5]. Recommendations regarding exercise, laboratory requirements for environment, equipment, staffing, and procedures have also been provided [4–6].

The Exercise Laboratory at Boston Children's Hospital has adopted many of these practices and has made modifications that best serve our pediatric and congenital heart disease (CHD) population. We have employed a model in which all cases are directly supervised by a master's level Exercise Physiologist with special in-house training in exercise testing for pediatric patients and patients with CHD. Higher-risk studies have direct physician supervision as well. All exercise tests are performed within a cardiology clinic suite, which allows for immediate assistance from nursing and physician staff for any adverse event that might occur during exercise testing. A code cart supplied with emergency drugs and a defibrillator, appropriate for the age and size of the patients studied, is always present in the lab. They are checked daily to ensure that they are up to date and in working condition. A call assist button, oxygen supply, and wall-mounted suction system are built into the laboratory and are readily available if/when needed. The exercise physiologists are certified in Pediatric Advanced Emergency Assessment, Recognition and Stabilization (PEARS), and Basic Life Support (BLS) and are trained to recognize and initiate interventions for emergency situations that call for a code team response. Adequate space is available for easy access to any patient who

T. J. Curran (✉)
Exercise Physiology, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: tracy.curran@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_8

might develop difficulties or require assistance while in the exercise laboratory.

To minimize risks, certain additional precautions are undertaken prior to testing. The exercise physiology staff prescreens all patients (usually on the day before a scheduled exercise test) prior to performing the test, to distinguish between patients at low risk and high risk for adverse events. Guidelines have been developed that stratify patients into risk categories based on our laboratory's clinical exercise testing experiences (Table 8.1) [3]. Pre-identified higher-risk patients, which represent about 10% of studies, have direct physician supervision (cardiology attending and/or fellow). It is recommended that individual institutions craft their own exercise testing policies as care patterns and resources available to the lab may vary. Our department has also instituted an alert notification procedure for any patient prescreened and identified as high risk. When a high-risk patient is identified, a "high-risk" team—comprised of the medical directors of the exercise lab, the administrative team, the clinic charge nurse, electrophysiology nurses, the exercise physiologists, and assigned cardiology fellows—is notified the day before the test is to occur (for previously scheduled patients) or as soon as the patient is identified (for same-day add-on patients). In addition, there is a daily "morning huddle" during which high-risk patients are discussed and communication with our intensive care unit (ICU) team is established.

The exercise physiology staff is also familiar with the exercise test termination criteria (Table 8.2) [5]. Cardiopulmonary parameters are monitored closely throughout the study, and clinical judgment is always used when making decisions regarding the termination or continuation of an exercise test.

Table 8.1 Pediatric patients at higher risk with exercise testing

Boston Children's Hospital High-risk criteria for exercise testing
Arrhythmia
Known exertional ventricular tachycardia
Catecholaminergic polymorphic ventricular tachycardia
Cardiomyopathy
Hypertrophic cardiomyopathy (excluding genotype positive, phenotype negative)
Dilated cardiomyopathy with moderate-to-severe ventricular dysfunction
More than mildly symptomatic restrictive cardiomyopathy
Cardiomyopathy with syncope
Congenital heart disease with:
Resting saturation ≤85%
Unrepaired cyanotic disease
Severe aortic stenosis (>80 mm Hg)
Severe pulmonary stenosis (>80 mm Hg)
Systemic/near-systemic RV pressure with moderate-to-severe RV dysfunction
Congenital heart disease with syncope (at the discretion of exercise lab staff)
Implantable cardioverter defibrillator
Pediatric coronary disease
Kawasaki's disease with significant coronary aneurysm
Angina/anginal equivalent symptoms
Pulmonary hypertension with:
≤90% desaturation at rest
>3/4 systemic pressure at rest
Recent history of syncope
Severe systemic ventricular dysfunction
Symptoms
Prior cardiac arrest without defibrillator
Exertional syncope with injury or incontinence and moderate suspicion for cardiac syncope

RV right ventricular

Table 8.2 Criteria for exercise test termination

1. Decrease in ventricular rate with increasing workload associated with extreme fatigue, dizziness, or other symptoms suggestive of insufficient cardiac output
2. Failure of heart rate to increase with exercise, and extreme fatigue, dizziness, or other symptoms suggestive of insufficient cardiac output
3. A fall in systolic blood pressure with increasing workload
4. Severe hypertension, >250 mm Hg systolic or 125 mm Hg diastolic, or blood pressures higher than that can be measured by the laboratory equipment
5. Chest pain suggestive of myocardial ischemia
6. Dyspnea that the patient finds intolerable
7. Symptomatic tachycardia that the patient finds intolerable
8. Progressive fall in oxygen saturation to <90% in a patient with normal oxygen saturation at rest, or a >10-point drop from resting saturation in a patient who is symptomatic
9. Presence of ≥3 mm flat or downward-sloping ST segment depression
10. Increasing ventricular ectopy with increasing workload, including a >3-beat run
11. Patient requests termination of the study

Source: American Heart Association, Inc. [5]

In a recent retrospective review of exercise tests performed at Boston Children's Hospital from 2013 to 2016 (5307 tests), we found that dangerous arrhythmias requiring intervention beyond simple termination of exercise were extremely rare (<0.1%) and that predefined high-risk criteria identified the three patients with the most serious events (i.e., those that required cardioversion/defibrillation or cardiopulmonary resuscitation). The serious events were recognized promptly. Effective interventions were quickly instituted and all patients had good outcomes. The absence of any high-risk criteria predicted a very low risk (negative predictive value 99.96; confidence intervals 99.92–100%) for arrhythmias requiring interventions beyond simple test termination [3].

Respect of the patient is of utmost importance before, during, and after exercise testing. An open discussion between staff, patient, and family should occur prior to any testing. This discussion should include what to expect during the exercise test, what the patient should report during the test, what we monitor during the test, and why the test might be terminated. Patients should also be informed that they may elect to terminate the exercise test at any point [4].

References

1. Ghosh RM, Gates GJ, Walsh CA, Schiller MS, Pass RH, Ceresnak SR. The prevalence of arrhythmias, predictors for arrhythmias, and safety of exercise stress testing in children. Pediatr Cardiol. 2015;36(3):584–90.
2. Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.
3. Barry OM, Gauvreau K, Rhodes J, Reichman J, Bourette LE, Curran TJ, et al. Incidence and predictors of clinically important and dangerous arrhythmias during exercise tests in pediatric and congenital heart patients. JACC Clin Electrophysiol. 2018;4(10):1319–27.
4. Taylor AL. Conducting the pediatric exercise test. In: Rowland TW, editor. Cardiopulmonary exercise testing in children and adolescents. Champaign: Human Kinetics; 2018. p. 13–20.
5. Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, et al. Clinical stress testing in the pediatric age group: a statement from the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth. Circulation. 2006;113(15):1905–20.
6. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873–934.

9 Special Considerations for Children

Jennifer L. Pymm

Introduction

Cardiopulmonary exercise testing (CPET) in children is often successful and informative, even in young children. However, to achieve success, a number of accommodations and special considerations will often be necessary. Basic pediatric exercise testing can begin as young as 4 years old, when indicated. CPET can be undertaken successfully in patients as young as 6 years old, although the maturity required to cooperate adequately for CPET is often not present until 8 years of age or older. For any given individual, the minimal age of compliance for an exercise test depends on the individual's maturity level, physical abilities, and often, the parent's support.

Pediatric Patients and Their Families

A unique situation in pediatric exercise testing compared to adult testing is having additional family members in the laboratory during testing. This should be considered when setting up the exercise laboratory. The laboratory should have space to accommodate families, but in an area that does not interrupt testing. During the initial explanation of the testing procedure, it is important to provide age-appropriate instructions and to focus on the patient as well as the parents/other family members. The child should be assured that the test will not hurt and can even be fun [1]. Often, the exercise test is the child's first opportunity to use exercise equipment (e.g., a treadmill or stationary bicycle); this novelty can and should be used to advantage, to help inspire interest and cooperation. Allowing time for questions from both the patient and their family is important and can avoid interruptions later during the test. Nevertheless, the exercise physiologist may find that, although time was allotted for questions prior to testing, parents will nevertheless interrupt and ask questions during the test. Acknowledging the parents, answering if one is able, and letting the parents know that questions will be answered at the end of the test are appropriate responses. During testing, primary focus should be on the child, their safety, and on obtaining the desired test data.

Test Equipment

CPET in pediatrics will also require adjustments to the equipment. Treadmills should have a lower handrail attachment that is accessible to smaller patients [1]. For younger patients, it can also be helpful to have additional staff available to "spot" the child on the treadmill and even stand behind

J. L. Pymm (✉)
Exercise Physiology, Department of Cardiology,
Boston Children's Hospital,
Boston, MA, USA
e-mail: jennifer.pymm@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_9

him/her, straddling the belt. Some younger patients may decide to stop abruptly or may be unsteady on the treadmill; spotting them closely maintains their safety. Cycle ergometers will also need pediatric adjustments, including handlebar, seat, and pedal shafts with the ability to adjust depending on the size of the patient [2]. Commonly, patients under 125–130 cm are unable to reach the pedals on the cycle ergometer even at the shortest pediatric adjustments and will need to be tested on the treadmill.

Other equipment considerations needed in pediatric exercise testing include smaller blood pressure cuffs, nose clip variety, and pediatric gowns [1]. Mouthpieces should be available in smaller sizes and masks of various sizes should be available in cases of mouthpiece intolerance. Adjustments can also be made with electrocardiogram (EKG) prepping procedures. EKG preparation typically includes alcohol and abrasive tape. For pediatric patients, alcohol is typically not necessary, and the abrasive tape should be used less aggressively. Avoiding aggressive prep is important because it can irritate the skin and cause a reaction that is uncomfortable for the patient and adversely affect their compliance.

When choosing a protocol for pediatric patients, there are several considerations. Treadmill protocols need to be used when a patient is too small for the cycle ergometer. Younger patients who fit on the cycle may have trouble maintaining a consistent cadence and/or stop inappropriately, or "when they feel like it" rather than when they are fatigued. Under these circumstances, a treadmill protocol may produce a better test result [1]. Patients who have relatively underdeveloped thigh muscles can fatigue earlier on the cycle ergometer versus the treadmill [2]. The Bruce protocol, most commonly used for treadmill testing, has 3 minute stages, which may be too long and boring for pediatric patients. Similarly, if the incremental increases in the stages of the protocol are too great, the child may terminate exercise prematurely and optimal data collection would not be possible [1]. It is often necessary to tailor the protocol, changing the speed and/or elevation of the treadmill on an individualized basis, in a manner that ideally accommodates the needs and capabilities of the patient. One of the greatest benefits of a cycle protocol is the ability to choose a ramping protocol appropriate for the patient's size and activity level. Cycle ergometer testing also allows for a more accurate assessment of maximum work rate, clearer EKG tracings, more reliable blood pressure measurements, and a lower risk for patient injury [3].

Imaging Studies

Imaging studies may be incorporated into pediatric exercise testing. Commonly employed modalities include nuclear medicine and echocardiographic imaging. If both methods provide comparable information, a stress echocardiogram is generally preferred by most pediatric patients. A stress echocardiogram is less invasive, less time-consuming, and does not require fasting or intravenous placement. These undesirable attributes of nuclear medicine tests are challenging for most children and could adversely affect their compliance and willingness to give a maximal effort on an exercise test.

Conclusion

Pediatric centers should have trained exercise physiologists, who possess knowledge of and experience with pediatric CPET. Under these circumstances, high-quality CPET can usually be achieved.

References

1. Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, Kimball TR, Knilans TK, Nixon PA, Rhodes J, Yetman AT. Clinical stress testing in the pediatric age group: a statement from the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth. Circulation. 2006;113(15):1905–20.
2. Skinner JS, editor. Exercise testing and exercise prescription for special cases: theoretical basis and clinical application. Philadelphia: Lippincott Williams & Wilkins; 1993.
3. Takken T, Bongers BC, Brussel M, Haapala EA, Hulzebos EHJ. Cardiopulmonary exercise testing in pediatrics. Ann Am Thorac Soc. 2017;14(Supplement 1):S123–8.

10 Special Considerations for Adults with Congenital Heart Disease

Jennifer L. Pymm

Introduction

Adults with congenital heart disease (CHD) require special considerations with regard to cardiopulmonary exercise testing. The major difference in testing adults with CHD versus testing adults with acquired heart disease is the indication for testing. In acquired heart disease, testing is usually undertaken to evaluate for myocardial ischemia. In adults with CHD, the reason for testing varies. However, its primary purpose is usually not the assessment of coronary artery disease, but more often focuses on precisely estimating aerobic functional capacity and assessing problems related to the underlying CHD. Hence, exercise physiologists who perform testing on adults with CHD should be familiar with the CHD anatomy and resulting pathophysiology; the various catheterization, surgical, and other strategies that have been used to treat the patient's CHD, the unique cardiovascular health issues that these patients may confront and how these issues may be exposed and assessed in the exercise laboratory.

Comorbidities

Compounding these complexities, as CHD patients age, new comorbidities related or unrelated to CHD often develop. The comorbidity most relevant to the exercise testing environment is acquired heart disease. Evaluation by an adult congenital heart disease specialist to rule out contraindications for testing and assess the risk: benefit ratio of the study should be undertaken prior to testing [1]. In most cases, if there is concern for active or unassessed coronary artery disease, this issue should be evaluated thoroughly prior to undertaking cardiopulmonary exercise testing (CPET).

Relying on electrocardiogram (EKG) changes to detect myocardial ischemia in adult CHD patients can be challenging, often misleading, and sometimes impossible because of baseline EKG abnormalities. In these cases, imaging studies may be required to more accurately assess for myocardial ischemia. When testing these patients, the exercise laboratory staff should be familiar with the signs and symptoms of myocardial ischemia and should be prepared to respond appropriately.

Exercise Testing

Adults with CHD are often tested in pediatric medical centers where children are also tested. This results in exercise physiologists testing

J. L. Pymm (✉)
Exercise Physiology Laboratory, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_10

patients from 4 years old through adulthood. It is important to employ age-appropriate testing explanations and motivation tactics. An adult patient should not be treated like a child. Ideally, adults with CHD should be tested in centers that are staffed with adult CHD physicians and exercise physiologists experienced both in CHD and in caring for adults [1].

With regard to the logistics of exercise testing, the approach to the adult patient with CHD is largely similar to that of the adult with acquired heart disease. Prepping the patient for testing and the equipment needed for testing are all similar. For example, prepping for electrode placement is done on adults by shaving when needed, alcohol prep and abrasive tape; these features do not vary depending on the adult population you are testing. The modality of testing (stationary cycle ergometer or treadmill) often depends on the exercise laboratory or physician preference. Most commonly, when performing cardiopulmonary exercise testing cycle ergometry is the preferred modality, as it allows assessment of work rate, provides better EKG recordings and permits more reliable auscultatory blood pressure measurements. It also carries a lower risk for fall injuries. Choosing a ramping protocol for an adult with CHD can, however, be challenging, particularly in overweight individuals. In these cases, one should consider the patient's previous CPET data (if available), lean body mass, age, activity level, and the patient's self-reported exercise capabilities to guide decisions regarding the optimal protocol.

Conclusion

In summary, exercise testing in adults with CHD requires specific knowledge, training, and approaches. These patients differ, in clinically important ways, from children with CHD and adults with acquired heart disease. Laboratories that possess these capabilities can safely acquire the valuable clinical information that is often accessible only through exercise testing.

Reference

1. Mantegazza V, Apostolo A, Hager A. Cardiopulmonary exercise testing in adult congenital heart disease. Ann Am Thorac Soc. 2017; 14(Supplement 1):S93–101.

Part III

Interpretation of the Cardiopulmonary Exercise Test

Peak Exercise Parameters

11

Jonathan Rhodes

Peak $\dot{V}_{O2}$

Peak $\dot{V}_{O2}$ is one of the most important and widely used cardiopulmonary exercise testing (CPET) indices of cardiovascular health [1]. For most normal individuals, and especially for those with cardiovascular disease, peak $\dot{V}_{O2}$ is limited by the amount of O_2 that the cardiopulmonary system can deliver to the exercising muscles. This in turn is limited by the circulatory system's ability to increase cardiac output during exercise. Hence, peak $\dot{V}_{O2}$ is an excellent indicator of the capabilities of a patient's cardiovascular system [2].

There is a subtle difference between peak $\dot{V}_{O2}$ and $\dot{V}_{O2max}$. If a subject expends an ideal effort on a progressive exercise test, she/he will come to a point where $\dot{V}_{O2}$ plateaus and an additional increment in work rate does not induce an additional increment in $\dot{V}_{O2}$. This plateau value is $\dot{V}_{O2max}$. Peak $\dot{V}_{O2}$, however, is merely the highest $\dot{V}_{O2}$ detected during an exercise test. Ideally, peak $\dot{V}_{O2}$ and $\dot{V}_{O2}$ max should be equal, but if a subject terminates exercise before reaching $\dot{V}_{O2max}$, the peak $\dot{V}_{O2}$ will be somewhat lower than $\dot{V}_{O2max}$.

The clinical value of peak $\dot{V}_{O2}$ often depends, to a large extent, upon an appreciation of what the normal value for peak $\dot{V}_{O2}$ might be. Unfortunately, for any individual patient, the determination of "normal" values for peak $\dot{V}_{O2}$ (in ml O_2/min) is not a straightforward undertaking. Peak $\dot{V}_{O2}$ varies with age; it tends to increase and reach a maximum during adolescence/early adulthood and decline progressively, by ~7%/decade, thereafter [3]. It also differs significantly between males and females, especially after puberty. Normal values for peak $\dot{V}_{O2}$ are also dependent upon body size; larger individuals can consume more oxygen than smaller individuals. The relationship between body mass and peak $\dot{V}_{O2}$ is, however, quite complicated. During exercise, adipose tissue consumes virtually no O_2 compared to skeletal muscle. Hence, merely normalizing peak $\dot{V}_{O2}$ for body mass ignores this important biologic fact and can be misleading. For instance, imagine a 50 kg individual who has a peak $\dot{V}_{O2}$ of 2000 ml/min (40 ml/kg/min). If this individual were to go on a high-calorie diet and gain an additional 50 kg of adipose tissue, without affecting his/her cardiopulmonary system, the peak $\dot{V}_{O2}$ would remain 2000 ml/min, but the weight-normalized peak $\dot{V}_{O2}$ would be only 20 ml/kg/min. This does not mean that the subject needs a heart transplant; it means she/he needs to lose weight!

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_11

The relationship between peak $\dot{V}_{O2}$ and body surface area, or other anthropomorphic measurements, is also complex. In recognition of these problems, and based upon theoretical considerations regarding the relationship between body size and peak $\dot{V}_{O2}$, some physiologists have suggested methods of normalizing peak $\dot{V}_{O2}$ using an exponent of body length or weight [4, 5]. There is no conformity of opinion concerning the optimal method, and these approaches invariably result in rather unwieldy and unfamiliar units (e.g., ml $O_2/kg^{2/3}$/min). Normalizing peak $\dot{V}_{O2}$ for lean body mass or skeletal muscle mass is theoretically appealing, but accurate estimation of these parameters is impractical and difficult outside of the research setting.

Hence, normal values for peak $\dot{V}_{O2}$ are usually calculated from prediction equations, based upon the 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 using a similar exercise protocol and from a population whose age and demographic background are similar to the patient's. For pediatric subjects, there are few studies that have generated these kinds of data. The most widely used prediction equations are drawn from the study of Cooper and Weiler-Ravell [6]. These investigators studied a group of 107 healthy children and adolescents 6–17 years old and generated prediction equations based upon gender and height (by relying on height, rather than weight, the potential confounding effects of adiposity/obesity upon the predictions are theoretically mitigated). The limitations of these prediction equations must, however, be recognized [1]. They tend to generate unrealistically low values for small children, especially boys [2]. Hence, for subjects <130 cm tall, it is usually best to calculate the predicted peak $\dot{V}_{O2}$, using the patient's ideal weight-for-height (as determined from a growth chart), and data from Cooper and Weiler-Ravell's study, which found that the peak $\dot{V}_{O2}$ of an average prepubescent boy was 42 ml/kg/min and for an average prepubescent girl was 38 ml/kg/min [6]. The height-based equations also tend to generate unrealistically high predicted values for tall, thin individuals. Therefore, for subjects with a body mass index (BMI) <19.0 kg/m^2, their weight-based equations are preferred [2, 6]. For subjects ≥18 years old, Jones' equation, which generates predictions based upon age, height, body mass, and gender (height is weighted much more heavily than body mass), [3] is theoretically appealing and has gained wide acceptance [7]. Wasserman's equation, based upon ideal body weight, is also widely used (albeit somewhat more cumbersome) and may have superior predictive power [8]. 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 [7]. In addition, it must be noted that the aforementioned equations were generated for subjects exercising on a cycle ergometer. When subjects exercise on a treadmill, they tend to achieve peak $\dot{V}_{O2}$ (and peak heart rate) ~5–10% higher than that on a cycle ergometer. A correction factor should therefore be employed if applying these equations to subjects who have performed a CPET on a treadmill.

Among children and adolescents, when comparing $\dot{V}_{O2}$ data from serial exercise tests separated by time intervals of more than ~6 months, it is especially important to focus upon % predicted values rather than absolute (ml/min) or weight-normalized values, in order to take into account the rapid growth (and concomitant increase in peak $\dot{V}_{O2}$) that normally occurs during the pediatric years. Similarly, among adults, when comparing serial studies separated by more than ~3 years, it is usually preferable to focus on % predicted values, as the prediction equations take into account the 7% per decade decline in peak $\dot{V}_{O2}$ that normally occurs with aging. When comparing data from serial tests performed over shorter time intervals, it is often best to compare absolute $\dot{V}_{O2}$ data. Similar considerations apply to other CPET parameters that are strongly affected by body size and/or age.

One may wonder whether peak $\dot{V}_{O2}$ is limited by the muscle cell mitochondria's ability to take up oxygen rather than the cardiopulmonary system's ability to deliver oxygen. In fact, however,

it seems that, except in cases of extreme debilitation or rare metabolic defects (e.g., Barth's syndrome), peak $\dot{V}_{O2}$ is limited by the supply of O_2 and not by the capacity of the mitochondria to reduce O_2 during oxidative phosphorylation. For instance, if O_2 delivery is enhanced by erythropoietin, blood doping, or high-altitude training, peak $\dot{V}_{O2}$ increases.

Measurements of peak $\dot{V}_{O2}$ have been found to possess important clinical implications for patients with pediatric and congenital heart disease (CHD). Peak $\dot{V}_{O2}$ has been found to be an independent predictor of death and/or hospitalization for patients with repaired tetralogy of Fallot [9], patients who have undergone atrial switch procedures for transposition of the great arteries [10], patients with pulmonary hypertension [11, 12], patients with congestive heart failure [13, 14], patients awaiting heart transplantation, [14] and patients with Fontan surgery [15–17].

Peak Work Rate and Endurance Time

The peak work rate is the highest work rate achieved by an individual during a progressive CPET employing a cycle ergometer. As with peak $\dot{V}_{O2}$, it is best to express the peak work rate as a % predicted value, based upon a prediction equation that takes into account age, gender, and body size. Because chemical energy is converted into mechanical energy with more or less the same efficiency in most normal individuals, the peak $\dot{V}_{O2}$ and peak work rate are usually closely linked. The clinical value of the peak work rate relates to the fact that it is one peak exercise parameter that is not measured directly by the metabolic cart and therefore can serve as an internal control against which the metabolic cart data can and should be compared. The peak work rate tends to be slightly more effort-dependent than the peak $\dot{V}_{O2}$ because, as mentioned previously, $\dot{V}_{O2}$ plateaus when an individual expends a maximal effort. Consequently, on an optimal exercise test, there is a brief, variable, and effort-dependent period before test termination when the work rate is increasing without a concomitant change in $\dot{V}_{O2}$.

Subjects with orthopedic or neurologic impairments that preclude efficient pedaling (or, more commonly, walking/running on a treadmill) must devote more energy, and therefore consume more oxygen, to overcome any level of resistance imposed by the ergometer. In contrast, individuals who predominantly engage in bicycle exercise may have a "training effect" and may be able to perform more work on a cycle ergometer for any given level of $\dot{V}_{O2}$ compared to individuals who do not engage in bicycle exercise. Similar considerations relate to runners and treadmill exercise. For treadmill-based CPETs (e.g., the Bruce protocol), the endurance time is the metric analogous to the peak work rate. Tables exist for estimating the normal endurance time on the Bruce protocol (Table 11.1) [18]. However, unlike the peak work rate, the endurance time is heavily influenced by other factors unrelated to cardiovascular function such as body weight (heavy individuals must expend much more energy to walk or run on an incline compared to lighter individuals), gait efficiency, how much the individual leans on the railings of the treadmill, etc. Consequently, compared to the peak work rate on a cycle ergometer, the range of normal values for the endurance time on a treadmill

Table 11.1 Endurance time on Bruce protocol for normal children with innocent murmurs

Age Group		Percentiles					
(year)	10	25	50	75	90	Mean	SD
Boys							
4–5	8.1	9.0	10.0	12.0	13.3	10.4	1.9
6–7	9.7	10.0	12.0	12.3	13.5	11.8	1.6
8–9	9.6	10.5	12.4	13.7	16.2	12.6	2.3
10–12	9.9	12.0	12.5	14.0	15.4	12.7	1.9
13–15	11.2	13.0	14.3	16.0	16.1	14.1	1.7
16–18	11.3	12.1	13.8	14.5	15.8	13.5	1.4
Girls							
4–5	7.0	8.0	9.0	11.2	12.3	9.5	1.8
6–7	9.5	9.6	11.4	13.0	13.0	11.2	1.5
8–9	9.9	10.5	11.0	13.0	14.2	11.8	1.6
10–12	10.5	11.3	12.0	13.0	14.6	12.3	1.4
13–15	9.4	10.0	11.5	12.0	13.0	11.1	1.3
16–18	8.1	10.0	10.5	12.0	12.4	10.7	1.4

Reprinted with permission from [18]

protocol is very broad, the relationship between endurance time and cardiovascular fitness is not as tight, and the utility of this parameter as an index of cardiopulmonary fitness, or as an internal control for metabolic cart data, is not as robust.

Heart Rate

During a progressive exercise test, heart rate (HR) increases linearly in proportion with $\dot{V}_{O2}$, from baseline levels to peak HR. The normal peak HR, for treadmill exercise, may be estimated from the equation [19]:

$$\text{Peak HR} = 220 - \text{age}(\text{years}) \qquad 11.1$$

Peak HR during cycle exercise tends to be 5–10% lower [19], so it is reasonable to multiply the predicted peak HR derived from this equation by 0.925 if a bicycle exercise protocol is employed.

Patients with sinus node dysfunction cannot increase their HRs to normal levels at peak exercise. In addition, the HR vs. $\dot{V}_{O2}$ 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 vs. $\dot{V}_{O2}$ relationship is elevated. Patients with impairment of both the chronotropic and stroke volume response to exercise may have "pseudonormalization" of the HR vs. $\dot{V}_{O2}$ 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 vs. $\dot{V}_{O2}$ relationship therefore appears depressed below the expected curve, but their peak HR is normal (Fig. 11.1) [2].

Recent adult studies have focused upon the heart rate reserve:

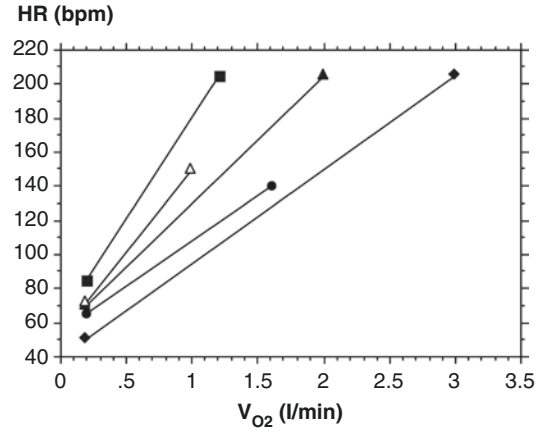


Fig. 11.1 Influence of various clinical conditions on the relationship between HR and $\dot{V}_{O2}$ during exercise. Variation of HR with respect to $\dot{V}_{O2}$ during a progressive exercise test for a hypothetical 50 kg, 15-year-old normal subject (solid triangle), athlete (diamond), patient with 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-$\dot{V}_{O2}$ 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 O_2P (i.e., stroke volume) to above-normal levels. (This pattern is also encountered in patients with structurally normal hearts who are receiving β[beta]-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 the stroke volume. This individual's peak $\dot{V}_{O2}$ is therefore more depressed than that of any of the other subjects. (Reprinted with permission from [47])

$$\text{peak HR} - \text{resting HR} \qquad 11.2$$

and the chronotropic index:

$$(100 \times (\text{HR reserve}) / (\text{predicted peak HR} - \text{resting HR}) \qquad 11.3$$

These indices have not been studied widely in pediatric patients, and their relevance to this population remains uncertain [20].

Chronotropic incompetence is common following surgery for congenital heart defect (CHD) [21–23] and has been associated with a poor prognosis [15, 23]. It is unclear, however, whether the observed relationship between chronotropic incompetence and mortality is due to the chronotropic incompetence per se or merely reflects the fact that many patients with arrhythmia problems (which have a negative impact on their prognosis) are on antiarrhythmic medications that inhibit the chronotropic response to exercise [15].

The Oxygen Pulse (O_2P)

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:

$$\dot{V}_{O2} / HR = O_2P = \left(\text{Cardiac Output} / HR\right) \times O_2\text{extraction} = \left(\text{Stroke Volume}\right) \times O_2\text{extraction} \quad 11.4$$

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 (the small amount of dissolved oxygen present under physiologic conditions can be ignored). Most patients with repaired CHDs have normal arterial O_2 saturations and normal hemoglobin concentrations. Furthermore, at peak exercise (and *only* 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 [24]. 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 [24–26]. Normal values for O_2P at peak exercise will, of course, be dependent upon patient size, age, and gender. Normal values may be calculated by dividing the predicted peak $\dot{V}_{O2}$ by the predicted peak HR. [7] It is important to note that the stroke volume referred to here is the "effective" stroke volume, i.e., amount of oxygenated blood ejected with each beat of the systemic ventricle that ultimately goes to the systemic circulation. Unlike the "angiographic" stroke volume, it does not include blood related to regurgitant or shunt lesions.

The limitations associated with the O_2P concept must be borne in mind when interpreting these data. In patients with depressed arterial O_2 content at peak exercise (e.g., 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 the stroke volume. In contrast, polycythemia increases the arterial O_2 content and would therefore cause the O_2P to overestimate the stroke volume. Similarly, conditions that impair the unloading of oxygen from hemoglobin (i.e., reduce oxygen extraction) will cause the mixed venous saturation to be abnormally high and will therefore cause the oxygen pulse to underestimate the stroke volume. This physiology is most commonly encountered in severe deconditioning, where atrophied muscles' ability to extract oxygen from hemoglobin is impaired. More rarely, other skeletal muscle abnormalities that impair oxygen extraction, such as glycogen storage diseases, mitochondrial and other metabolic defects (e.g., Barth's syndrome), some toxins (e.g., carbon monoxide), or rare

hemoglobinopathies that cause an increased affinity of hemoglobin for oxygen (i.e., cause the hemoglobin-oxygen dissociation curve to be shifted leftward), will also cause the O_2P to be depressed and to underestimate 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, in the absence of other cardiovascular problems, the O_2P at peak exercise should be elevated (Fig. 11.1). 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 distortion of the tight relationship between the stroke volume and O_2P at peak exercise that is caused by right-to-left intracardiac shunting can be appreciated from Eq. 11.2. When blood from which the (physiologic) maximal amount of oxygen has been extracted happens to shunt right to left and get pumped back to the body, the fraction of SV comprised by this blood does not increase the O_2P. The S_aO_2 and S_vO_2 of the right-to-left shunting blood will be equivalent (i.e., no additional oxygen can be extracted from this blood), and the $(S_aO_2 - S_vO_2)$ term in Eq. 11.4 will, for this blood, equal zero. Hence, although right-to-left shunting blood contributes fully to the stroke volume at peak exercise, it contributes nothing to the O_2P. Similarly, when partially desaturated blood (e.g., from pulmonary venous desaturation) is pumped into the systemic circulation, the desaturated blood increases the O_2P by a correspondingly smaller amount, and the relationship between the O_2P and the SV is also distorted.

During a progressive (upright) exercise test, there is a rapid initial increase in O_2P, primarily due to an increase in stroke volume. Thereafter, the more gradual increase in O_2P is due primarily to increased oxygen extraction. Under no circumstances, however, should the O_2P decline during exercise. A decline in O_2P may be seen in patients with myocardial ischemia secondary to coronary artery disease, cardiomyopathy, and/or severe outflow tract obstruction.

The O_2P at peak exercise 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 systolic or diastolic function, severe obstructive lesions, severe valvular regurgitation, coronary artery disease/myocardial ischemia, pulmonary, or systemic vascular disease often have a low peak-exercise O_2P [11, 12, 14, 25–29].

The O_2P is often depressed in patients who have undergone a Fontan procedure, even in the absence of ventricular or valvular dysfunction. Indeed, the O_2P is one of the strongest correlates of peak work rate in patients with Fontan circulations [20]. 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. Consequently, the Fontan patient's ventricle may be markedly underfilled (preload restricted) during exercise.

Young patients with chronic aortic regurgitation usually have well-preserved exercise function and peak-exercise O_2P [27, 30]. 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 apply to patients with isolated pulmonary insufficiency, where the decline in pulmonary vascular resistance during exercise mitigates the effects of the incompetent pulmonary valve, and right ventricular dilation can, over time, compensate for the volume load imposed by the pulmonary regurgitation. Hence, patients with isolated pulmonary insufficiency (e.g., patients with pulmonary stenosis s/p successful pulmonary valvuloplasty) typically have normal, or near normal, exercise function [31]. Similar physiologic mechanisms may also help to preserve the exercise function of patients with other valvular insufficiency lesions.

Respiratory Exchange Ratio (RER)

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 regarding 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 $\dot{V}_{CO2}$ over $\dot{V}_{O2}$. Unlike the respiratory quotient described in Chap. 1, which is a theoretical concept based upon the stoichiometry of the chemical equations involved in the aerobic metabolism of the fuels that the body uses to support its metabolic activities, the RER is a measured parameter that reflects not only the CO_2 produced by the aerobic metabolism of fuels but also the CO_2 produced from the buffering of lactic acid by bicarbonate and the variations in CO_2 excretion related to transient changes in the body's CO_2 stores (i.e., hyperventilation or hypoventilation). At rest, the RER is usually determined primarily by stoichiometry. (It may, however, be distorted by the alterations in CO_2 excretion associated with hyperventilation or hypoventilation.) As discussed earlier, for the aerobic metabolism of carbohydrates, 1 mole of CO_2 is produced for every mole of O_2 that is consumed; for fats, 1 mole of CO_2 is produced for every 1.5 moles of O_2 consumed. Hence, at rest, the RER is usually about 0.85 (i.e., somewhere between 0.67 and 1.00). During a progressive exercise test, as the anaerobic threshold is surpassed and an increasing fraction of the energy required by the exercising muscles is derived from anaerobic metabolism, $\dot{V}_{CO2}$ rises out of proportion to $\dot{V}_{O2}$, and the RER rises progressively. An RER >1.09 is considered to be compatible with a good effort or, more specifically, that exercise termination was (at least partly) due to lactate accumulation secondary to a heavy reliance upon anaerobic metabolism to meet the energy needs of the exercising muscles [32]. (Some investigators believe that the anaerobic metabolic pathways are less developed in children and therefore feel that for young subjects an RER $\geq$1.05 is a more appropriate threshold [33, 34].) 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. Under these circumstances, peak exercise parameters may not accurately reflect the capabilities of the cardiovascular system and must therefore be interpreted cautiously.

The most common cause for a low RER at peak exercise is a suboptimal effort. Patients with severe lung disease may also have a low RER at peak exercise because their ability to increase CO_2 excretion is impaired and cannot keep up with the high CO_2 production associated with more strenuous exercise. This results in CO_2 retention and elevated arterial pCO_2 levels. Exercise terminates on account of the resulting respiratory acidosis, rather than lactic acid accumulation. Orthopedic pain (e.g., a sore knee or sprained ankle) may cause a subject to stop exercising at a relatively low exercise intensity, before there is significant lactate accumulation or RER elevation. Patients with certain rare metabolic defects (e.g., glycogen storage diseases) in which lactic acid production is impaired will have a low RER at peak exercise. Patients with neuromuscular diseases and/or severe debilitation may stop exercising due to profound muscle weakness rather than lactic acid accumulation and may therefore have a low peak-exercise RER.

Within a few seconds after the termination of exercise, a steep rise in the RER is typically encountered. The physiology underlying this phenomenon is a reflection of the different mechanisms by which O_2 and CO_2 are transported in the blood and the obligate decline in cardiac output that occurs upon the termination of exercise secondary to the abrupt loss of the skeletal muscles' pumping action (see Chaps. 2, 3 and 4). Oxygen delivery to the muscles, which is dependent on the cardiac output and the arterial O_2 content of the blood (which in turn is determined by the arterial O_2 saturation and the hemoglobin concentration), falls in parallel with the decline in cardiac output (hemoglobin levels do not change upon termination of exercise and, of course, arterial O_2 saturation cannot rise above 100%). In contrast, CO_2 delivery from the mus-

cles to the lungs is relatively well maintained because, unlike O_2, the CO_2 content of the blood is not limited by the binding of CO_2 to hemoglobin. The CO_2 content of the venous blood returning to the lungs from the muscles *can therefore rise* following the termination of exercise and at least partially compensate for the decline in cardiac output. Hence, CO_2 delivery to and excretion by the lungs does not decline as much as the O_2 delivery to and consumption by the muscles. The RER (CO_2 excretion divided by O_2 consumption) therefore rises.

Blood Pressure

During a progressive exercise test, systolic blood pressure tends to rise progressively, whereas diastolic blood pressure changes little compared to the baseline, resting values. The increase in systolic blood pressure is more pronounced in older, larger individuals. It is also higher in males. In the pediatric age group, however, it is rare for the systolic blood pressure at peak exercise to exceed 200 mm Hg in males and 180 mm Hg in females. Nomograms describing the normal blood pressure response to exercise, based on body surface area and gender, are available (see Fig. 3.1) [35, 36].

As a rule of thumb, the systolic blood pressure at peak exercise should exceed resting values by at least 20% or 20 mm Hg. Many congenital heart defects, in which the cardiac output response to exercise is depressed, may have a blunted blood pressure response to exercise. Under no circumstances should the systolic blood pressure fall during exercise (except when there is baseline anticipatory hypertension related to anxiety). A decline in systolic blood pressure may be seen in patients with hypertrophic cardiomyopathy, severe ventricular dysfunction, severe ventricular outflow obstruction, and myocardial ischemia. It is an ominous prognostic sign and in many contexts an indication for terminating an exercise test.

An excessive rise in blood pressure may be seen in patients with coarctation of the aorta, even following "successful repair." [37] This may be due to subtle residual arch obstruction, in which case a significant upper-lower extremity blood pressure (cuff) gradient may be detected [38]. The presence of an arch obstruction can also be documented/confirmed with an immediate postexercise Doppler echocardiography. Some patients with repaired aortic coarctations may have hypertension during exercise, even in the absence of a residual arch obstruction. This may be related to abnormal arterial compliance, elevated systemic vascular resistance, or abnormalities of baroreceptor function and/or the renin angiotensin system [39].

It may be seen from the previous discussion that exercise is normally associated with an increase in the pulse pressure: ΔP; systolic bold pressure minus diastolic blood pressure. This reflects the increase in stroke volume during exercise. This physiology is best understood from a rearrangement of the compliance equation:

$$\Delta P = \Delta V / \text{compliance} = \left(\text{stroke volume}\right) / \left(\text{arterial compliance}\right) \qquad 11.5$$

This equation readily conveys the fact that conditions that are associated with an impaired stroke volume response to exercise will have lower-than-normal pulse pressure during exercise. In contrast, individuals with a higher-than-normal stroke volume response to exercise (e.g., athletes, patients with aortic regurgitation, or patients with an isolated chronotropic defect) will have an increased pulse pressure. In addition, patients with reduced arterial compliance (e.g., patients with aortic coarctations) will have increased pulse pressures.

Arterial O_2 Saturation

Oxygen does not diffuse across the alveolar-capillary membrane as rapidly as CO_2. Nevertheless, in normal individuals exercising at, or near, sea level, the diffusion of O_2 is rapid

enough to fully saturate the hemoglobin in the red blood cells leaving the alveolus (i.e., pulmonary venous O_2 saturation and consequently, in the absence of a right-to-left shunt, systemic arterial oxygen saturation approach 100%), even at peak exercise, when capillary transit time is maximally reduced [40]. In patients with pulmonary vascular disease, however, the capillary transit time may be markedly reduced as the blood is forced to flow through the restricted vascular bed. In severe cases, the capillary transit time may be so brief that pO_2 of the blood does not have time to equilibrate with the pO_2 of the alveolus, resulting in pulmonary venous and systemic arterial desaturation. Similar physiology may apply to patients with large intracardiac left-to-right shunts, although I am unaware if this has ever been convincingly demonstrated in the exercise physiology laboratory.

Lesions that cause intrapulmonary right-to-left shunting (e.g., atelectasis) or that impair gas exchange across the alveolar-capillary membrane (e.g., congenital alveolar proteinosis) will also result in pulmonary venous and systemic arterial desaturation.

Patients with (potential or actual) right-to-left intracardiac shunts may develop progressive systemic arterial desaturation during exercise [41–43] via two mechanisms: (1) depending on the physiology present, the magnitude of the right-to-left shunt may increase during exercise; and/or (2) because mixed venous O_2 saturation progressively declines during exercise, the blood shunting right to left during exercise will have a lower oxygen saturation and will therefore lower the systemic arterial O_2 saturation even if the magnitude of the right-to-left shunt remains unchanged.

Respiratory Measurements

Many patients with congenital heart disease have coexistent lung disease due to congenital anomalies, injuries related to cardiovascular disease (e.g., recurrent pneumonias and respiratory infections), and/or its treatments (e.g., cardiothoracic surgeries, prolonged intubation, etc.) [44]. These issues are often overlooked by pediatric and congenital cardiologists. The respiratory data from a CPET can provide clinically important insights into this dimension of a patient's cardiopulmonary status, and an analysis of these data should be incorporated into every exercise test. Some of these relevant peak-exercise respiratory parameters will now be reviewed.

Assessment of a patient's "breathing reserve" at peak exercise permits clinicians to infer whether a patient's exercise capacity is limited by cardiovascular or respiratory factors. This assessment is based upon an estimation of a patient's maximal voluntary ventilation (MVV). This parameter is determined by encouraging a subject to breathe in and out as rapidly and deeply as she/he can for 12 seconds, measuring how many liters of air have been exhaled during this maneuver and multiplying that value by 5. Conceptually, it is the theoretical maximum amount of air an individual can breathe out during a minute. It has been found that normal subjects at peak exercise typically utilize only ~65% of their MVV, and they therefore have a "breathing reserve" of approximately 35%. For this reason, most exercise physiologists conclude that, at peak exercise, normal subjects are cardiovascularly (rather than respiratorily) limited. This conclusion implies that normal people stop exercising because their cardiovascular system cannot provide sufficient blood flow/oxygen to meet the metabolic demands of their muscles; lactate therefore accumulates within the muscles, the muscles fatigue, and exercise cannot continue. They do not stop exercising on account of an inability to breathe, since the MVV maneuver demonstrates that under some circumstances the subjects can breathe more than they do at peak exercise [45]. Their sense of breathlessness at peak exercise may be related to fatigue of their muscles of respiration, but is not due to an intrinsic inability to ventilate their lungs further. Patients with isolated (or predominant) cardiovascular disease will have a higher-than-normal breathing reserve because they will tend to have a relatively normal MVV but cannot raise their metabolic rate to normal levels. In contrast, patients with predominant lung disease (e.g., cystic fibrosis) will have a low MVV but will use all, or almost all, of their MVV at peak exercise and will have little or no breathing reserve.

The MVV maneuver is very effort dependent, and most children (as well as many older subjects) cannot perform it properly. It has been found, however, that in subjects who perform a good MVV maneuver, their MVV may be estimated by the equation [46]:

$$\mathrm{MVV} = \mathrm{FEV1} \times 40. \qquad 11.6$$

Consequently, in most cases, it is our practice to use this equation to estimate the MVV and calculate the breathing reserve.

As mentioned earlier, tidal volume typically increases during exercise, reaching levels of ~45–65% of a subject's baseline forced vital capacity. In patients with obstructive pulmonary physiology and air trapping, tidal volume at peak exercise tends to be smaller than normal and comprises a smaller percentage of the baseline forced vital capacity. In patients with restrictive pulmonary physiology, baseline forced vital capacity tends to be reduced, and the tidal volume at peak exercise tends to comprise a larger-than-normal percentage of the forced vital capacity.

In normal individuals, the respiratory rate at peak exercise rarely exceeds 60 breaths per minute at peak exercise. It is often higher in patients with restrictive and/or obstructive lung physiology, as they may be unable to increase their tidal volumes normally during exercise and compensate by increasing their respiratory rate. Children tend to have higher respiratory rates at peak exercise compared to adolescents and adults. Anxiety can also cause subjects to have rapid, shallow breaths during exercise.

It may be seen from the prior discussion that basic spriometric measurements (FVC, FEV1, etc.) are needed to properly contextualize and interpret the respiratory data obtained during a CPET. Consequently, baseline spirometry should always be acquired prior to a CPET study.

Acknowledgment Portions of this chapter were based upon the author's previously published works:

- Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.
- Rhodes J. Exercise testing. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Elsevier; 2006.

References

1. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873–934.
2. Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.
3. Jones NL, Summers E, Killian KJ. Influence of age and structure on exercise during incremental cycle ergometry in men and women. Am Rev Respir Dis. 1989;140:1373–80.
4. Rogers DM, Olson BL, Wilmore JH. Scaling for the VO2-to-body size relationship among children and adults. J Appl Physiol. 1995;79(3):958–67.
5. Jones NL. Clinical exercise testing. 4th ed. Philadelphia: W. B. Saunders; 1997. p. 132–2.
6. Cooper DM, Weiler-Ravell D. Gas exchange response to exercise in children. Am Rev Respir Dis. 1984;129(2:Pt 2):S47–8.
7. Anonymous. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211–77.
8. Arena R, Myers J, Abella J, Pinkstaff S, Brubaker P, Moore B, et al. Determining the preferred percent-predicted equation for peak oxygen consumption in patients with heart failure. Circ Heart Fail. 2009;2(2):113–20.
9. Giardini A, Specchia S, Tacy TA, Coutsoumbas G, Gargiulo G, Donti A, et al. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of fallot. Am J Cardiol. 2007;99:1462–7.
10. Giardini A, Hager A, Lammers AE, Derrick G, Muller J, Diller GP, et al. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. J Am Coll Cardiol. 2009;53(17):1548–55.
11. Arena R, Lavie CJ, Milani RV, Myers J, Guazzi M. Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. J Heart Lung Transplant. 2010;29:159–73.
12. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken G, Kleber FX, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation. 2002;106(3):319–24.

13. Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2)slope and peak VO(2). Eur Heart J. 2000;21(2):154–61.
14. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83(3):778–86.
15. Fernandes SM, Alexander ME, Graham DA, Khairy P, Rodriguez E, Pearson DD, et al. Ability of exercise testing to predict morbidity and mortality in adults with Fontan surgery. Congenit Heart Dis. 2011;6:294–303.
16. Egbe AC, Driscoll DJ, Khan AR, Said SS, Akintoye E, Berganza FM, et al. Cardiopulmonary exercise test in adults with prior Fontan operation: the prognostic value of serial testing. Int J Cardiol. 2017;235:6–10.
17. Diller GP, Giardini A, Dimopoulos K, Gargiulo G, Muller J, Derrick G, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. Eur Heart J. 2010;31(24):3073–83.
18. Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. Am J Cardiol. 1978;41(1):69–75.
19. Braden DS, Carroll JF. Normative cardiovascular responses to exercise in children. Pediatr Cardiol. 1999;20(1):4–10.
20. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li J, et al. A cross-sectional study of exercise performance during the first two decades of life following the Fontan operation. J Am Coll Cardiol. 2008;52:99–107.
21. Reybrouck T, Weymans M, Stijns H, Van der Hauwaert LG. Exercise testing after correction of tetralogy of Fallot: the fallacy of a reduced heart rate response. Am Heart J. 1986;112(5):998–1003.
22. McCrindle BW, Zak V, Sleeper LA, Paridon SM, Colan SD, Geva T, et al. Laboratory measures of exercise capacity and ventricular characteristics and function are weakly associated with functional health status after Fontan procedure. Circulation. 2010;121(1):34–42.
23. Diller GP, Dimopoulos K, Okonko D, Uebing A, Broberg CS, Babu-Narayan S, et al. Heart rate response during exercise predicts survival in adults with congenital heart disease. J Am Coll Cardiol. 2006;48(6):1250–6.
24. Stringer WW, Hansen JE, Wasserman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. J Appl Physiol (1985). 1997;82(3):908–12.
25. Jones NL. Clinical exercise testing. 4th ed. Philadelphia: W.B. Saunders; 1997. p. 135.
26. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. Philadelphia: Lippincott; 1999. p. 151.
27. Rhodes J, Fischbach PS, Patel H, Hijazi ZM. Factors affecting the exercise capacity of pediatric patients with aortic regurgitation. Pediatr Cardiol. 2000;21(4):328–33.
28. Kipps AK, Graham DA, Lewis E, Marx GR, Banka P, Rhodes J. Natural history of exercise function in patients with Ebstein anomaly: a serial study. Am Heart J. 2012;163(3):486–91.
29. Meadows J, Powell AJ, Geva T, Dorfman A, Gauvreau K, Rhodes J. Cardiac magnetic resonance imaging correlates of exercise capacity in patients with surgically repaired tetralogy of Fallot. Am J Cardiol. 2007;100(9):1446–50.
30. Kipps AK, McElhinney DB, Kane J, Rhodes J. Exercise function of children with congenital aortic stenosis following aortic valvuloplasty during early infancy. Congenit Heart Dis. 2009;4(4):258–64.
31. Harrild DM, Powell AJ, Trang TX, Geva T, Lock JE, Rhodes J, et al. Long-term pulmonary regurgitation following balloon valvuloplasty for pulmonary stenosis: risk factors and relationship to exercise capacity and ventricular volume and function. J Am Coll Cardiol. 2010;55(10):1041–7.
32. Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. J Magn Reson Imaging. 2003;17:323–9.
33. Rowland TW. Aerobic exercise testing protocols. In: Rowland TW, editor. Pediatric laboratory exercise testing: clinical guidelines. Champaign: Human Kinetics; 1993. p. 33–4.
34. Hansen HS, Froberg K, Nielsen JR, Hyldebrandt N. A new approach to assessing maximal aerobic power in children: the Odense School Child Study. Eur J Appl Physiol Occup Physiol. 1989;58(6):618–24.
35. Alpert BS, Flood NL, Strong WB, Dover EV, DuRant RH, Martin AM, et al. Responses to ergometer exercise in a healthy biracial population of children. J Pediatr. 1982;101(4):538–45.
36. Riopel DA, Taylor AB, Hohn AR. Blood pressure, heart rate, pressure-rate product and electrocardiographic changes in healthy children during treadmill exercise. Am J Cardiol. 1979;44(4):697–704.
37. Hauser M. Exercise blood pressure in congenital heart disease and in patients after coarctation repair. Heart. 2003;89(2):125–6.
38. Freed MD, Rocchini A, Rosenthal A, Nadas AS, Castaneda AR. Exercise-induced hypertension after surgical repair of coarctation of the aorta. Am J Cardiol. 1979;43(2):253–8.
39. Hauser M, Kuehn A, Wilson N. Abnormal responses for blood pressure in children and adults with surgically corrected aortic coarctation. Cardiol Young. 2000;10(4):353–7.
40. Presson RG Jr, Graham JA, Hanger CC, Godbey PS, Gebb SA, Sidner RA, et al. Distribution of pulmonary capillary red blood cell transit times. J Appl Physiol (1985). 1995;79(2):382–8.

41. Dimopoulos K, Okonko DO, Diller GP, Broberg CS, Salukhe TV, Babu-Narayan SV, et al. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation. 2006;113(24):2796–802.
42. Fernandes SM, McElhinney DB, Khairy P, Graham DA, Landzberg MJ, Rhodes J. Serial cardiopulmonary exercise testing in patients with previous Fontan surgery. Pediatr Cardiol. 2010;31(2):175–80.
43. Inuzuka R, Diller GP, Borgia F, Benson L, Tay ELW, Alonso-Gonzalez R, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation. 2012;125:250–9.
44. Alonso-Gonzalez R, Borgia F, Diller GP, Inuzuka R, Kempny A, Martinez-Naharro A, et al. Abnormal lung function in adults with congenital heart disease: prevalence, relation to cardiac anatomy, and association with survival. Circulation. 2013;127(8):882–90.
45. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. Philadelphia: Lippincott Wiliams & Wilkins; 1999.
46. Campbell SC. A comparison of the maximum voluntary ventilation with the forced expiratory volume in one second: an assessment of subject cooperation. J Occup Med. 1982;24(7):531–3.
47. Rhodes J. Ch 16. Exercise testing. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Elsevier; 2006. p. 275–87.

12 Parameters from Submaximal Exercise

Jonathan Rhodes

Ventilatory Anaerobic Threshold (VAT)

As discussed earlier in this book, during a progressive exercise test, the anaerobic threshold (theoretically) 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 physiologic 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 cardiovascular system's capacity 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 $\dot{V}_{CO2}$ out of proportion to the associated increase in $\dot{V}_{O2}$. This phenomenon can be detected by expiratory gas analysis. The $\dot{V}_{O2}$ at this point is termed the "VAT" [1–4].

A number of methods may be employed to identify the VAT during a progressive exercise test (Fig. 12.1). If $\dot{V}_{CO2}$ is plotted vs. $\dot{V}_{O2}$, an inflection point is observed at the VAT, reflecting the disproportionate increase in $\dot{V}_{CO2}$ that occurs secondary to the buffering of lactic acid by bicarbonate [5]. Alternatively, the VAT can be identified as the point in time when the ratio of minute ventilation over $\dot{V}_{O2}$ (the $\dot{V}_E/\dot{V}_{O2}$ ratio) begins to increase, while the $\dot{V}_E/\dot{V}_{CO2}$ ratio is flat or declining. The reason for this phenomenon can be understood from Eq. 4.1 from Chap. 4, which indicates that alveolar ventilation ($\dot{V}_A$, which is the dominant component of $\dot{V}_E$) increases in proportion with $\dot{V}_{CO2}$. Hence, if $\dot{V}_{CO2}$ increases due to anaerobic metabolism, $\dot{V}_E$ increases in parallel and the $\dot{V}_E/\dot{V}_{CO2}$ ratio does not change. (The $\dot{V}_E/\dot{V}_{CO2}$ ratio may actually decline during this phase of exercise because ventilation/perfusion matching improves and physiologic dead space declines as pulmonary artery pressure increases, allowing more blood to flow to the previously underperfused apices of the lungs (i.e., West Zone 1; see Chap. 3). However, because the $\dot{V}_{O2}$ does not increase as rapidly as the $\dot{V}_{CO2}$ beyond the VAT, the $\dot{V}_E/\dot{V}_{O2}$ ratio begins to rise. This method of identifying the VAT is worthwhile because it can readily distinguish between hyperventilation (e.g., due to anxiety), which leads to increases in both the $\dot{V}_E/\dot{V}_{O2}$ and the

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_12

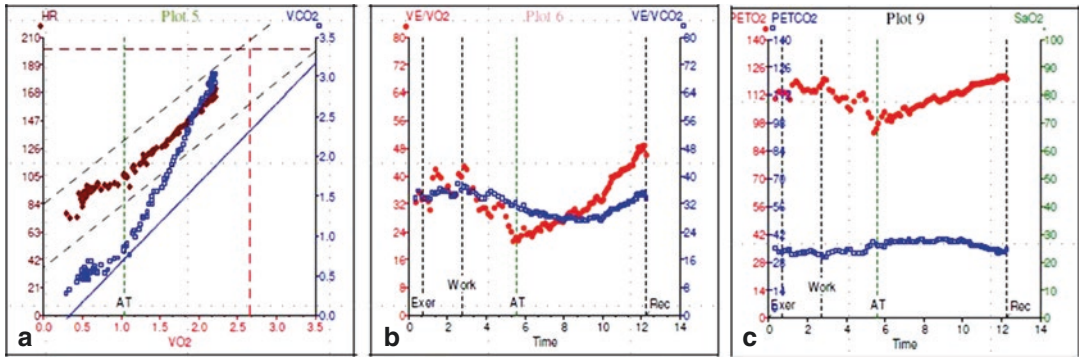


Fig. 12.1 Methods for determining the ventilator anaerobic threshold (VAT). (**a**) When $\dot{V}_{CO2}$ is plotted vs. $\dot{V}_{O2}$, an inflection point is observed at the VAT. (**b**) The ratio of minute ventilation over $\dot{V}_{O2}$ (the $\dot{V}_E/\dot{V}_{O2}$ ratio) begins to increase, while the $\dot{V}_E/\dot{V}_{CO2}$ ratio is flat or declining. (**c**) End-tidal pO_2 reaches a minimum and begins to rise. Figure (**c**) also depicts a typical end-tidal pCO_2 vs. time curve during a progressive exercise test. After some initial anticipatory hyperventilation, when the end-tidal pCO_2 is somewhat less than 40 mm Hg, the end-tidal pCO_2 rises to ~40 mm Hg (prior to the VAT). It remains at that level until the respiratory compensation point (after the VAT) when the end-tidal pCO_2 falls, reflecting the respiratory alkalosis that develops in compensation for the accumulating lactic (metabolic) acidosis. AT ventilatory anaerobic threshold, Exer exercise, HR heart rate, $PETCO_2$ end-tidal pCO_2, $pETO_2$ end-tidal pO_2, Rec recovery, VE/VCO_2 ratio of minute ventilation to carbon dioxide production, VE/V_{O2} ratio of minute ventilation to oxygen consumption, VCO_2 carbon dioxide production, V_{O2} oxygen consumption

$\dot{V}_E/\dot{V}_{CO2}$ ratios, and the VAT, which is characterized by an increase in the $\dot{V}_E/\dot{V}_{O2}$ ratio but not the $\dot{V}_E/\dot{V}_{CO2}$ ratio [3]. Finally, the VAT may also be identified as the point in time when the end-tidal pO_2 begins to rise. Once again, this phenomenon arises because the increased $\dot{V}_A$ associated with the VAT brings more air (and oxygen) per time interval into the alveolus. Since the $\dot{V}_{O2}$ does not increase as much as the $\dot{V}_A$, there is more O_2 left in the alveolus at the end of each breath, and the end-tidal pO_2 rises [6].

The $\dot{V}_{O2}$ at the VAT is *clinically* relevant because it reflects the level of oxygen delivery beyond which the circulatory system is no longer able to completely fulfill the metabolic needs (i.e., ATP requirements) of the exercising muscles. The VAT therefore may convey important information regarding the health and capabilities of the circulatory system. Moreover, the anaerobic threshold is a physiologically determined phenomenon. Unlike peak exercise parameters, it is not affected by a subject's effort or motivation [1, 2].

One can infer from the aforementioned discussion that some subjectivity exists regarding the determination of the VAT. This introduces a degree of uncertainty into the measurement that should be borne in mind when interpreting VAT data.

Any cardiovascular condition that impairs the delivery of oxygen to the exercising muscles will tend to lower the anaerobic threshold. This includes obstructive lesions, regurgitant lesions, shunt lesions, disorders of systolic or diastolic function, absence of a pulmonary ventricle, pulmonary vascular disease, peripheral vascular disease (e.g., coarctation of the aorta, Takyasu's arteritis), chronotropic defects, and rhythm disturbances that impair atrioventricular synchrony. Patients with Barth's syndrome tend to have extremely low anaerobic thresholds because their mitochondria cannot take up oxygen normally, and they therefore rely more heavily on anaerobic metabolism for the generation of ATP [7]. For similar reasons, patients with other rare mitochondrial defects in which the oxidation of fuels is partially uncoupled from the generation of ATP also have low anaerobic thresholds. In contrast, patients with glycogen storage diseases and other conditions that impair the generation of lactate often do not have a detectable VAT, nor does the respiratory exchange ratio (RER) rise to normal

levels at peak exercise, even when they expend a maximal effort [8].

Prediction equations exist for the calculation of normal values for the VAT on the basis of age, size, and gender [9]. VAT is also commonly expressed as a percentage of predicted peak $\dot{V}_{O2}$. In the absence of cardiovascular disease, VAT rarely falls below 40% of the predicted peak $\dot{V}_{O2}$. 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 [3]. In children with congenital heart disease (CHD), the VAT is often depressed in a manner similar to, albeit milder than, the peak $\dot{V}_{O2}$ [10]. Hence, when reliable peak $\dot{V}_{O2}$ data are available, VAT data does not often provide significant additional clinical information. However, if a patient does not expend an optimal effort and does not achieve an RER $\geq$1.09 at peak exercise (and therefore has peak exercise parameters that may be unreliable indicators of a patient's cardiovascular function), the VAT can provide a valuable window into the patient's cardiovascular health. Identification of the VAT is also worthwhile because the heart rate (HR) at the VAT has been recommended as the target HR for rehabilitation training [4].

Among patients who cannot augment their forward stroke volume normally during exercise, the $\dot{V}_{O2}$ at the VAT tends to be less affected than the peak $\dot{V}_{O2}$ because she/he can compensate for the stroke volume deficit by increasing his/her heart rate more rapidly than normal during submaximal exercise and thereby maintain relatively normal O_2 delivery. However, the patient cannot increase the peak HR beyond normal peak values and therefore is unable to compensate for the stroke volume deficit at peak exercise. Similar considerations apply to patients with chronotropic defects.

$\dot{V}_E/\dot{V}_{CO2}$ Slope

Empirically, it has been observed that $\dot{V}_E$ rises linearly in proportion with $\dot{V}_{CO2}$ 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 $\dot{V}_{CO2}$. The $\dot{V}_E/\dot{V}_{CO2}$ 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 additional liters of air that must be breathed out in order to eliminate one additional liter of CO_2 [11]. The point where the $\dot{V}_E/\dot{V}_{CO2}$ slope begins to deviate from linearity has been termed the "respiratory compensation" point [6].

Some physiologists choose to measure the $\dot{V}_E/\dot{V}_{CO2}$ slope from the data throughout exercise, including points beyond the respiratory compensation point. This practice is probably misguided. As an individual exercises beyond the respiratory compensation point, more and more data points are generated that deviate further and further from the linear portion of the $\dot{V}_E$ vs. $\dot{V}_{CO2}$ relationship. The $\dot{V}_E/\dot{V}_{CO2}$ slope therefore becomes an effort-dependent parameter—a property that is particularly undesirable when seeking to apply these $\dot{V}_E/\dot{V}_{CO2}$ slope data to clinical situations.

The normal value for the $\dot{V}_E/\dot{V}_{CO2}$ slope is somewhat age dependent (Fig. 12.2). In older adolescents and young adults, it should be less than 28. Thereafter, gas exchange within the lungs gradually becomes more inefficient (as does almost everything with age) and normal values rise. The $\dot{V}_E/\dot{V}_{CO2}$ slope also tends to be higher in children and younger adolescents [12]. The reason for this observation probably relates to the fact that lung volumes (and hence the tidal volume during exercise) increase rapidly during childhood and adolescence, much more rapidly than the anatomic dead space volume. Hence, the dead space/tidal volume ratio declines during the pediatric years. As indicated by Eq. 4.4 in Chap. 4, this physiologic development results in less ventilation for any given level of $\dot{V}_{CO2}$. The $\dot{V}_E/\dot{V}_{CO2}$ slope is often elevated in patients with tetralogy of Fallot (TOF), [13], congestive heart failure (CHF) [14, 15], atrial switch procedures [16], and pulmonary hypertension [17, 18]. In these patients, $\dot{V}_E/\dot{V}_{CO2}$ slope elevation has been associated with an increased risk of mortality. Although multiple factors may influence the $\dot{V}_E/\dot{V}_{CO2}$ slope, among patients with pediatric and congenital heart disease, pulmonary blood flow maldistribu-

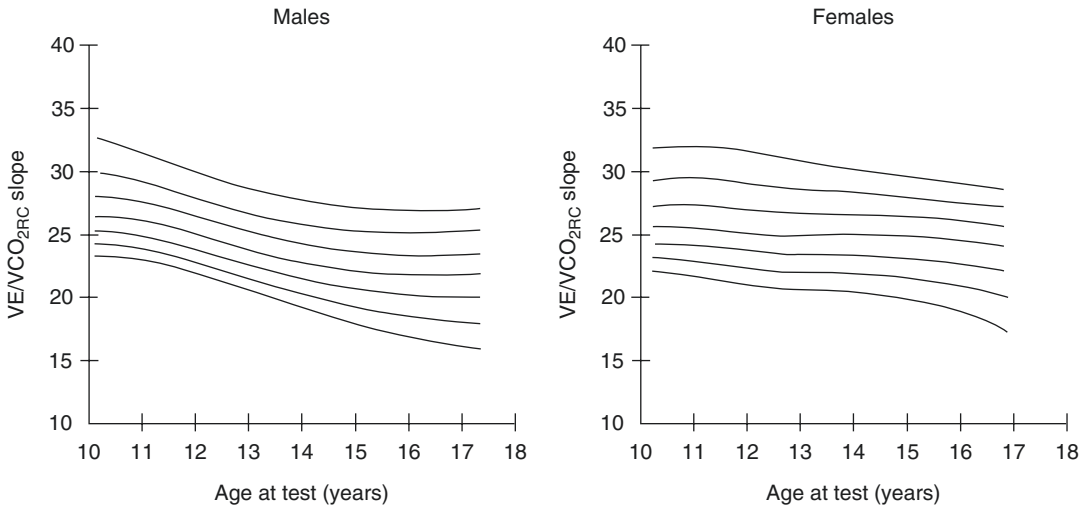


Fig. 12.2 Percentiles for $\dot{V}_E/\dot{V}_{CO2}$ slope in normal male and female children, respectively. The slopes were calculated from the data up to the respiratory compensation point. (Reprinted with permission from [12])

tion and consequent ventilation/perfusion (V/Q) mismatch are probably the most important pathophysiologic processes that underlie these observations and associations [4, 19, 20].

Efficient gas exchange across the alveolar/capillary membrane requires optimal V/Q matching. Patients who have undergone repair of TOF often have residual pulmonary artery stenoses that cause PBF misdistribution, which in turn has been linked to $\dot{V}_E/\dot{V}_{CO2}$ slope elevation and depressed peak $\dot{V}_{O2}$ [19, 21, 22]. These stenoses can have a particularly deleterious effect upon the physiology of the postoperative tetralogy patient and a strong, negative impact upon a patient's prognosis. Effective relief of these stenoses has been associated with improvements in peak $\dot{V}_{O2}$ and the $\dot{V}_E/\dot{V}_{CO2}$ slope (see Chap. 14) [22].

If you ask a radiologist to identify the earliest sign of congestive heart failure detectable on a chest X-ray, she/he would probably say "cephalization of pulmonary blood flow" (which is the result of the elevation of the left atrial and pulmonary capillary wedge pressure). To an exercise physiologist, this radiologic finding implies pulmonary blood flow maldistribution. As the CHF worsens and the pulmonary capillary wedge pressure rises, more fluid enters the alveolar capillary membrane, gas exchange is further impaired, and the $\dot{V}_E/\dot{V}_{CO2}$ slope rises further. As the CHF worsens and the pulmonary capillary wedge pressure rises yet higher, frank pulmonary edema develops, gas exchange is further impaired, and the $\dot{V}_E/\dot{V}_{CO2}$ slope rises still further. Hence, in patients with CHF, a strong link between pulmonary capillary wedge pressure and the $\dot{V}_E/\dot{V}_{CO2}$ slope probably accounts for the prognostic power of the $\dot{V}_E/\dot{V}_{CO2}$ slope that has been observed in this patient population. In a similar manner, for patients who have had an atrial switch procedure for the transposition of the great arteries (TGA), elevation of the $\dot{V}_E/\dot{V}_{CO2}$ slope probably reflects the progressive systemic (right) ventricular dysfunction that often develops in these patients as they age.

In patients with pulmonary hypertension, pulmonary blood flow (PBF) maldistribution results from pulmonary vascular obstructive disease. As the vascular obstruction progresses, the PBF maldistribution worsens, gas exchange within the lungs becomes more and more inefficient, and the $\dot{V}_E/\dot{V}_{CO2}$ slope rises. Hence, for patients with this condition, the $\dot{V}_E/\dot{V}_{CO2}$ slope reflects the extent of disease within the pulmonary vasculature [17, 18]. (This physiology may also be relevant to TGA patients who develop pulmonary vascular obstructive disease after an atrial switch procedure.)

The $\dot{V}_E/\dot{V}_{CO2}$ slope is also almost always elevated in patients with Fontan procedures [23].

Once again, this observation is probably due, to a large extent, to PBF maldistribution (and associated V/Q mismatch) secondary to the absence of a pulmonary ventricle [24, 25]. In Fontan patients, however, the degree of $\dot{V}_E/\dot{V}_{CO2}$ slope elevation is not associated with increased mortality because, in contrast to the conditions enumerated earlier, the elevated slope is intrinsic to the patients' single ventricle physiology and not necessarily related to the progression/severity of the underlying cardiovascular disease process [4, 26].

Right-to-left intracardiac or intrapulmonary shunting will also cause the $\dot{V}_E/\dot{V}_{CO2}$ 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 arterial chemoreceptors, inducing central nervous system respiratory centers to increase the patient's respiratory drive (and $\dot{V}_E$) and causing the $\dot{V}_E/\dot{V}_{CO2}$ 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 (e.g., by closing a Fontan patient's fenestration; see Chap. 15) almost always produces a reduction in the $\dot{V}_E/\dot{V}_{CO2}$ slope [4, 27].

The $\dot{V}_E/\dot{V}_{CO2}$ slope will also be elevated in patients with interstitial lung disease—a condition that may occasionally be encountered in patients with pediatric and congenital heart disease. The interstitial lung disease impairs gas exchange across the alveolar capillary membrane. Patients will therefore have to breathe more to excrete any given amount of CO_2, and their $\dot{V}_E/\dot{V}_{CO2}$ slope will be elevated.

Patients with obstructive (and to a lesser extent, restrictive) lung disease will tend to have low $\dot{V}_E/\dot{V}_{CO2}$ slopes. The lung disease will limit the patient's capacity to increase $\dot{V}_E$ during exercise. CO_2 excretion may, however, be *relatively* well maintained if there is a concomitant increase in alveolar pCO_2 (see Eq. 4.1 in Chap. 4), and the $\dot{V}_E/\dot{V}_{CO2}$ slope will therefore be depressed. In patients with a coexistent lung disease and V/Q mismatch secondary to a cardiovascular problem, the $\dot{V}_E/\dot{V}_{CO2}$ slope depression secondary to the lung disease may offset the elevation that results from V/Q mismatch, and "pseudonormalization" of the $\dot{V}_E/\dot{V}_{CO2}$ slope may be observed.

Some investigators have used the $\dot{V}_E/\dot{V}_{CO2}$ ratio (generally at the VAT) as an index of gas exchange efficiency instead of the $\dot{V}_E/\dot{V}_{CO2}$ slope. Although both parameters reflect more or less the same physiology, there is much more variability in the $\dot{V}_E/\dot{V}_{CO2}$ ratio, because it is determined from a single data point rather than the slope of a linear relationship. Normal values for the $\dot{V}_E/\dot{V}_{CO2}$ ratio are also less well established. The use of this parameter in place of the more standard $\dot{V}_E/\dot{V}_{CO2}$ slope should therefore be avoided, when possible.

End-Tidal pCO_2

Because CO_2 diffuses easily across the alveolar-capillary membrane, the alveolar pCO_2 rapidly comes into equilibrium with the pCO_2 of the blood leaving the alveolus. Hence, in the absence of shunts or inhomogeneous ventilation/perfusion (V/Q) matching, end-tidal pCO_2 closely matches arterial pCO_2 [28, 29]. Consequently, the end-tidal pCO_2 should be ~40 mm Hg at rest and during early phases of a progressive exercise test. However, as the exercise intensity increases beyond the VAT and a lactic (metabolic) acidosis develops, homeostatic mechanisms come into play and cause individuals to increase their ventilation, lower their arterial pCO_2, and generate compensatory respiratory alkalosis (see Chap. 4). This process will be reflected by a decline in the end-tidal pCO_2 (Fig. 12.1c).

Many patients will be anxious or have "anticipatory hyperventilation" prior to and during the early phases of cardiopulmonary exercise testing (CPET). End tidal pCO_2 levels below 40 mm Hg are therefore commonly encountered during these phases of a CPET. However, most individuals will cease hyperventilating within 2 or 3 minutes of the initiation of exercise, and their pCO_2 levels will rise to ~40 mm Hg until after the VAT, when they begin to decline once again on account of the compensatory respiratory alkalosis that develops in response to the lactic acidosis.

In fit individuals who are able to achieve high exercise intensities and metabolic rates, end-tidal

pCO_2 will tend to exceed arterial pCO_2 at higher levels of exercise [29, 30]. This observation relates to the fact that the arterial pCO_2 reflects the average pCO_2 of blood leaving the alveolus over the course of a breath. Because CO_2 diffusion is so rapid and the pCO_2 within the alveolus comes into equilibrium with the blood so quickly, at rest and during lighter exercise intensities, the alveolar pCO_2 rapidly plateaus and the alveolar pCO_2 toward the end of the breath does not differ significantly from the alveolar pCO_2 near the beginning of the breath. Consequently, the blood leaving the alveolus has approximately the same pCO_2 throughout the respiratory cycle and the end-tidal pCO_2 closely matches the arterial pCO_2. However, at higher levels of exercise intensity, the quantity of CO_2 delivered to the alveolus is so great that the alveolar pCO_2 does not plateau; it rises continually over the course of the breath. Hence, blood leaving the alveolus early in the course of a breath will have a lower pCO_2 (generally less than 40 mm Hg) than blood leaving the alveolus toward the end of the breath. The end-tidal pCO_2 reflects the blood leaving the alveolus at the end of the breath, and will therefore exceed the arterial pCO_2, which reflects the average pCO_2 of blood leaving the alveolus. Hence, it is not unusual to observe end-tidal pCO_2 levels >40 mm Hg at high levels of exercise intensity in fit individuals. However, even under these circumstances, a *decline* in end-tidal pCO_2 levels at higher levels of exercise, beyond the "respiratory compensation point", should always be observed. In contrast, patients with severe lung disease may be unable to excrete all of the CO_2 their muscles are producing at higher levels of exercise. Consequently, their arterial and end-tidal pCO_2 levels will rise and the decline in end-tidal pCO_2 that normally occurs beyond the respiratory compensation point will not be observed.

Abnormally low end-tidal pCO_2 levels are commonly observed in patients with congenital heart disease. This phenomenon is not due to low arterial pCO_2. It is typically due to right-to-left shunting and/or V/Q mismatch. The physiology underlying each of these mechanisms will now be discussed.

As discussed in Chap. 4, venous pCO_2 levels rise dramatically during exercise, reaching levels of 60 mm Hg or higher. Hence, when blood shunts right to left during exercise, it is not only low in oxygen content; it is also high in CO_2 content. The elevated CO_2 levels would be sensed by chemoreceptors in the aorta and arch vessels and trigger homeostatic mechanisms to correct this imbalance by increasing alveolar ventilation and driving down pCO_2 levels in the alveolus and the blood leaving the alveolus (i.e., the pulmonary venous blood). The pulmonary venous pCO_2 levels will decline to levels somewhat below 40 mm Hg, so that when this blood mixes with the CO_2-rich right-to-left shunting blood, the resultant mixture, in the aorta and systemic arteries, would have a pCO_2 of 40 mm Hg. Under these circumstances the end-tidal pCO_2 will be low (and lower than the arterial pCO_2), reflecting the low alveolar pCO_2 [4, 27].

In patients with V/Q mismatch, the air leaving alveoli with low perfusion would tend to have low pCO_2. For instance, in the extreme case of an alveolus with ventilation but no perfusion, the air leaving the alveolus will have a pCO_2 of 0 mm Hg (i.e., equivalent to room air) because the air in that alveolus would not have participated in gas exchange. The low pCO_2 air from the underperfused alveoli will dilute out the CO_2 in air coming from other alveoli. The end tidal pCO_2 will therefore be low, lower than the arterial pCO_2, which, of course, in the absence of a right-to-left shunt, reflects the pCO_2 of blood returning from perfused alveoli [4, 21, 22].

Oxygen Uptake Efficiency Slope

Empirically it has been observed that there is a linear relationship between $\dot{V}_{O2}$ and log $\dot{V}_E$. The slope of this relationship is termed the oxygen uptake efficiency slope (OUES). In patients who expend a good effort, the OUES has been found to correlate closely with the peak $\dot{V}_{O2}$. Because determination of the OUES does not require a peak effort, it has been advocated as a good submaximal index of exercise function. The OUES is, however, somewhat effort dependent;

estimates of the OUES generated from the first 75% of an exercise test are significantly lower than values obtained when data from all of exercise is included [31].

In tests where the peak $\dot{V}_{O2}$ data is reliable, the OUES probably does not add important clinical information. Its prognostic power has also been found to be inferior to the $\dot{V}_E/\dot{V}_{CO2}$ slope in patients with congestive heart failure [32]. However, in tests where a peak effort is not expended, the OUES can, because of its strong correlation with peak $\dot{V}_{O2}$, provide worthwhile insights into a patient's cardiopulmonary function (in some populations). It must also be noted that the OUES has been studied primarily in adults with acquired heart disease. Experience with children is limited. Moreover, as with peak $\dot{V}_{O2}$, the OUES is strongly dependent upon age, size, and gender [33]. These issues may be *partially* mitigated by normalizing the OUES for body surface area [34]. However, as discussed previously, in patients with congenital heart disease, one may encounter physiologic anomalies (e.g., right-to-left shunts, pulmonary artery stenoses) uncommon among adults with acquired heart disease that may influence the relationship between $\dot{V}_{O2}$ and $\dot{V}_E$ and disrupt the tight correlation between the OUES and peak $\dot{V}_{O2}$ [35].

Oxygen Uptake-Work Rate Relationship: $\Delta\dot{V}_{O2}/\Delta WR$

In most people, chemical energy is converted into mechanical energy with more or less the same efficiency. Hence, after an initial delay near the onset of work and until the $\dot{V}_{O2}$ plateaus near $\dot{V}_{O2max}$, there is a linear relationship between the $\dot{V}_{O2}$ and the work rate. The slope of this linear portion of the $\dot{V}_{O2}$-work rate relationship is termed the "$\Delta\dot{V}_{O2}/\Delta WR$." In normal individuals, the value of the $\Delta\dot{V}_{O2}/\Delta WR$ is 10.3 ± 1.0 ml/min/watt. In patients with impaired oxygen delivery to the muscles, a greater proportion of the energy required by the muscles is derived from anaerobic metabolism, and the $\Delta\dot{V}_{O2}/\Delta WR$ is low [36]. Hence, cyanotic patients and patients with impairment of the cardiac output response to exercise will have a low $\Delta\dot{V}_{O2}/\Delta WR$. Among patients encountered in the field of pediatric cardiology, a disproportionately low $\Delta\dot{V}_{O2}/\Delta WR$ may also be encountered in patients with coarctation of the aorta [37] or peripheral vascular disease secondary to Takyasu's arteritis. In contrast, individuals who cannot pedal efficiently (e.g., on account of neurologic or emotional issues) will tend to have an elevated $\Delta\dot{V}_{O2}/\Delta WR$. Similarly, obese individuals may have to expend more-than-normal amounts of energy to move their heavy limbs and chest walls during exercise and therefore may also have an elevated $\Delta\dot{V}_{O2}/\Delta WR$. Of course, the issue of unmeasured energy expenditure in obese subjects is even more relevant with treadmill exercise, as that modality requires them to carry their entire body weight, rather than resting most of it on the seat of a cycle ergometer.

The Exercise Electrocardiogram

Analysis of exercise electrocardiogram (EKG) data is an integral component of an exercise test. The influence of exercise on the incidence and nature of rhythm disturbances should be assessed. In structurally normal hearts, ectopy that is suppressed by exercise is thought to be benign [38]. In contrast, myocardial ischemia, cardiomyopathies, and conditions such as the prolonged QT syndrome and catecholamine-sensitive ventricular tachycardia are often characterized by an increase in the frequency and complexity of ectopy during exercise [39]. Rhythm disturbances are also commonly encountered in patients who have had surgery for congenital heart disease. In these patients, the absence or suppression of an arrhythmia during an exercise test may have little predictive value. However, patients whose arrhythmias develop or worsen with exercise appear to be at greater risk for future serious arrhythmic events, and exercise testing therefore plays an important role in the assessment and management of this difficult clinical issue [39].

The influence of exercise on conduction abnormalities should also be assessed. Patients with significant AV nodal disease may develop progressively higher grade AV block during exer-

cise. In contrast, patients with AV block secondary to elevated resting vagal tone (e.g., many athletes) typically develop normal AV conduction during exercise [40]. In patients with Wolff-Parkinson-White syndrome (WPW), the sudden loss of pre-excitation during exercise is thought to indicate that the bypass tract has a relatively long anterograde effective refractory period and that the subject is therefore at low risk for sudden cardiac death [41, 42]. Indeed, this finding on an exercise EKG functions as a key decision point within the Pediatric and Congenital Electrophysiology Society's and the Heart Rhythm Society's suggested algorithm for the management of asymptomatic patients with WPW [42]. Patients with the prolonged QT syndrome may have normal QT intervals at rest but may be unable to shorten their QT interval appropriately during exercise [43, 44]. In patients with pacemakers, analysis of the exercise EKG may help assess whether the pacemaker is functioning properly and whether the pacemaker settings are optimal [45]. These topics are discussed in greater detail in Part V of this textbook.

The influence of exercise on the ST segment and T-wave morphology should also be analyzed. It must be emphasized, however, that the incidence of coronary artery disease in the pediatric population is quite low, whereas baseline ST-T abnormalities and/or bundle branch blocks (which render the interpretation of ST-T changes less reliable) are common. Consequently, the sensitivity and specificity of ST-T wave changes for the detection of coronary artery anomalies in pediatric subjects are unknown (but probably are not very good) [46–48]. Exercise-induced ST-T wave changes are more commonly encountered in pediatric patients with cardiomyopathies and/or myocardial ischemia secondary to excessively high myocardial oxygen demand during exercise (e.g., patients with aortic stenosis). More severe ST-T changes are certainly more suggestive of myocardial ischemia, especially when associated with chest pain and other abnormalities [46, 49, 50]. However, the correlation between ST-T changes and myocardial ischemia in pediatric patients, although not precisely known, is probably no more than moderate [51, 52]. Radionuclide-based myocardial perfusion imaging is often employed to help in the assessment of patients thought to be at increased risk for myocardial ischemia and has been found to be helpful in patients with Kawasaki disease [53] and hypertrophic cardiomyopathy [54]. However, perfusion abnormalities of questionable clinical significance, unassociated with significant detectable coronary artery pathology, are commonly found in patients following the arterial switch operation [48]. The value of myocardial perfusion studies in patients with congenital coronary artery malformations has also not been established.

Acknowledgment Portions of this chapter were based upon the author's previously published works:

- Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.
- Rhodes J. Exercise testing. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Elsevier; 2006.

References

1. Wasserman K. Determinants and detection of anaerobic threshold and consequences of exercise above it. Circulation. 1987;76(Supp VI)(6:Pt 2):VI-29-VI-39.
2. Wasserman K. The Dickinson W. Richards lecture. New concepts in assessing cardiovascular function. Circulation. 1988;78(4):1060–71.
3. Wasserman K. The anaerobic threshold measurement to evaluate exercise performance. Am Rev Respir Dis. 1984;129(2:Pt 2):t-40.
4. Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.
5. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol. 1986;60(6):2020–7.
6. Wasserman K, Hansen DA, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. 3rd ed. Philadelphia: Lippincott; 1999.
7. Spencer CT, Byrne BJ, Bryant RM, Margossian R, Maisenbacher M, Breitenger P, et al. Impaired cardiac reserve and severely diminished skeletal muscle O(2) utilization mediate exercise intolerance in Barth syndrome. Am J Physiol Heart Circ Physiol. 2011;301(5):H2122–9.
8. Tarnopolsky M. Exercise testing in metabolic myopathies. Phys Med Rehabil Clin N Am. 2012;23(1):173–86, xii

9. Cooper DM, Weiler-Ravell D. Gas exchange response to exercise in children. Am Rev Respir Dis. 1984;129(2:Pt 2):S47–8.
10. Rhodes J. Exercise testing. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. Philadelphia: Elsevier; 2006. p. 275–87.
11. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. Philadelphia: Lippincott; 1999. p. 173–4.
12. Giardini A, Odendaal D, Khambadkone S, Derrick G. Physiologic decrease of ventilatory response to exercise in the second decade of life in healthy children. Am Heart J. 2011;161(6):1214–9.
13. Giardini A, Specchia S, Tacy TA, Coutsoumbas G, Gargiulo G, Donti A, et al. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of fallot. Am J Cardiol. 2007;99:1462–7.
14. Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol. 1997;29(7):1585–90.
15. Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2)slope and peak VO(2). Eur Heart J. 2000;21(2):154–61.
16. Giardini A, Hager A, Lammers AE, Derrick G, Muller J, Diller GP, et al. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. J Am Coll Cardiol. 2009;53(17):1548–55.
17. Arena R, Lavie CJ, Milani RV, Myers J, Guazzi M. Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. J Heart Lung Transplant. 2010;29:159–73.
18. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken G, Kleber FX, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation. 2002;106(3):319–24.
19. Buller NP, Poole-Wilson PA. Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. Br Heart J. 1990;63(5):281–3.
20. Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chua TP, Davos CH, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation. 2001;103(7):967–72.
21. Rhodes J, Dave A, Pulling MC, Geggel RL, Marx GR, Fulton DR, et al. Effect of pulmonary artery stenoses on the cardiopulmonary response to exercise following repair of tetralogy of fallot. Am J Cardiol. 1998;81(10):1217–9.
22. Sutton NJ, Peng L, Lock JE, Lang P, Marx GR, Curran TJ, et al. Effect of pulmonary artery angioplasty on exercise function after repair of tetralogy of fallot. Am Heart J. 2008;155(1):182–6.
23. Troutman WB, Barstow TJ, Galindo AJ, Cooper DM. Abnormal dynamic cardiorespiratory responses to exercise in pediatric patients after Fontan procedure. J Am Coll Cardiol. 1998;31(3):668–73.
24. Grant GP, Mansell AL, Garofano RP, Hayes CJ, Bowman FO Jr, Gersony WM. Cardiorespiratory response to exercise after the fontan procedure for tricuspid atresia. Pediatr Res. 1988;24(1):1–5.
25. Matsushita T, Matsuda H, Ogawa M, Ohno K, Sano T, Nakano S, et al. Assessment of the intrapulmonary ventilation-perfusion distribution after the fontan procedure for complex cardiac anomalies: relation to pulmonary hemodynamics. J Am Coll Cardiol. 1990;15(4):842–8.
26. Fernandes SM, Alexander ME, Graham DA, Khairy P, Rodriguez E, Pearson DD, et al. Ability of exercise testing to predict morbidity and mortality in adults with Fontan surgery. Congenit Heart Dis. 2011;6:294–303.
27. Meadows J, Lang P, Marx 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(2):108–13.
28. Jones NL, McHardy GJ, Naimark A, Campbell EJ. Physiological dead space and alveolar-arterial gas pressure differences during exercise. Clin Sci. 1966;31(1):19–29.
29. Whipp BJ, Wasserman K. Alveolar-arterial gas tension differences during graded exercise. J Appl Physiol. 1969;27(3):361–5.
30. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. Philadelphia: Lippincott; 1999. p. 82.
31. Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. J Am Coll Cardiol. 1996;28(6):1567–72.
32. Arena R, Myers J, Hsu L, Peberdy MA, Pinkstaff S, Bensimhon D, et al. The minute ventilation/carbon dioxide production slope is prognostically superior to the oxygen uptake efficiency slope. J Card Fail. 2007;13(6):462–9.
33. Marinov B, Mandadzhieva S, Kostianev S. Oxygen-uptake efficiency slope in healthy 7- to 18-year-old children. Pediatr Exerc Sci. 2007;19(2):159–70.
34. Tsai YJ, Li MH, Tsai WJ, Tuan SH, Liao TY, Lin KL. Oxygen uptake efficiency slope and peak oxygen consumption predict prognosis in children with tetralogy of fallot. Eur J Prev Cardiol. 2016;23(10):1045–50.
35. Giardini A, Specchia S, Gargiulo G, Sangiorgi D, Picchio FM. Accuracy of oxygen uptake efficiency slope in adults with congenital heart disease. Int J Cardiol. 2009;133(1):74–9.
36. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. 3rd ed. Philadelphia: Lippincott; 1999.
37. Rhodes J, Geggel RL, Marx GR, Bevilacqua L, Dambach YB, Hijazi ZM. Excessive anaerobic

metabolism during exercise after repair of aortic coarctation. J Pediatr. 1997;131(2):210–4.
38. Jacobsen JR, Garson A Jr, Gillette PC, McNamara DG. Premature ventricular contractions in normal children. J Pediatr. 1978;92:36–8.
39. Wiles HB. Exercise testing for arrhythmia: children and adolescents. Prog Pediatr Cardiol. 1993;2(2):51–60.
40. Jones NL. Clinical exercise testing. 4th ed. Philadelphia: W.B. Saunders; 1997.
41. Bricker JT, Porter CJ, Garson A Jr, Gillette PC, McVey P, Traweek M, et al. Exercise testing in children with Wolff-Parkinson-White syndrome. Am J Cardiol. 1985;55(8):1001–4.
42. Cohen MI, Triedman JK, Cannon BC, Davis AM, Drago F, Janousek J, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS). Heart Rhythm. 2012;9(6):1006–24.
43. Vincent GM, Jaiswal D, Timothy KW. Effects of exercise on heart rate, QT, QTC and QT/QS2 in the Romano-Ward inherited long QT syndrome. Am J Cardiol. 1991;68(5):498–503.
44. Weintraub RG, Gow RM, Wilkinson JL. The congenital long QT syndromes in childhood. J Am Coll Cardiol. 1990;16(3):674–80.
45. Bricker JT, Garson A Jr, Traweek MS, Smith RT, Ward KA, Vargo TA, et al. The use of exercise testing in children to evaluate abnormalities of pacemaker function not apparent at rest. Pacing Clin Electrophysiol. 1985;8(5):656–60.
46. James FW, Kaplan S, Glueck CJ, Tsay JY, Knight MJ, Sarwar CJ. Responses of normal children and young adults to controlled bicycle exercise. Circulation. 1980;61(5):902–12.
47. Mahle WT, McBride MG, Paridon SM. Exercise performance after the arterial switch operation for d-transposition of the great arteries. Am J Cardiol. 2001;87(6):753–8.
48. Weindling SN, Wernovsky G, Colan SD, Parker JA, Boutin C, Mone SM, et al. Myocardial perfusion, function and exercise tolerance after the arterial switch operation. J Am Coll Cardiol. 1994;23(2):424–33.
49. Shimizu M, Ino H, Okeie K, Emoto Y, Yamaguchi M, Yasuda T, et al. Exercise-induced st-segment depression and systolic dysfunction in patients with nonobstructive hypertrophic cardiomyopathy. Am Heart J. 2000;140(1):52–60.
50. Yetman AT, Hamilton RM, Benson LN, McCrindle BW. Long-term outcome and prognostic determinants in children with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1998;32(7):1943–50.
51. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873–934.
52. Kane DA, Fulton DR, Saleeb S, Zhou J, Lock JE, Geggel RL. Needles in hay: chest pain as the presenting symptom in children with serious underlying cardiac pathology. Congenit Heart Dis. 2010;5(4):366–73.
53. Hijazi ZM, Udelson JE, Snapper H, Rhodes J, Marx GR, Schwartz SL, et al. Physiologic significance of chronic coronary aneurysms in patients with Kawasaki disease. J Am Coll Cardiol. 1994;24(7):1633–8.
54. Dilsizian V, Bonow RO, Epstein SE, Fananapazir L. Myocardial ischemia detected by thallium scintigraphy is frequently related to cardiac arrest and syncope in young patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1993;22(3):796–804.

Putting It All Together

13

Jonathan Rhodes

In order to derive the maximum value from the wealth of data generated by a cardiopulmonary exercise test (CPET), it is important to approach the analysis of the data in a systematic manner (Fig. 13.1). The first question that should be addressed is: Did the patient expend an adequate effort and do the peak exercise data accurately reflect his/her capabilities? To answer this question, one should examine the respiratory exchange ratio (RER) data. If the RER rises consistently during the later phases of exercise and ultimately exceeds 1.09, it is likely that the patient expended a good effort and that exercise was terminated at, or near, the cardiovascular limit [1]. One should also seek data to support this conclusion. For instance, if there was a plateau in the $\dot{V}_{O2}$ vs. time curve near the end of exercise, the peak V_{O2} was probably equivalent to the $\dot{V}_{O2}$ max; if the peak heart rate approached the predicted peak heart rate (in the absence of a tachyarrhythmia), it probably was a near-maximal effort (although the opposite is not true, since many patients have chronotropic issues and cannot achieve a normal peak heart rate). One should also take into account subjective impressions of the patient's efforts and recognize that there are conditions where exercise is limited by non-cardiovascular factors (e.g., orthopedic issues/pain, severe pulmonary disease, certain rare metabolic disorders), which may cause a patient to terminate exercise without achieving a high RER, despite expending a good effort.

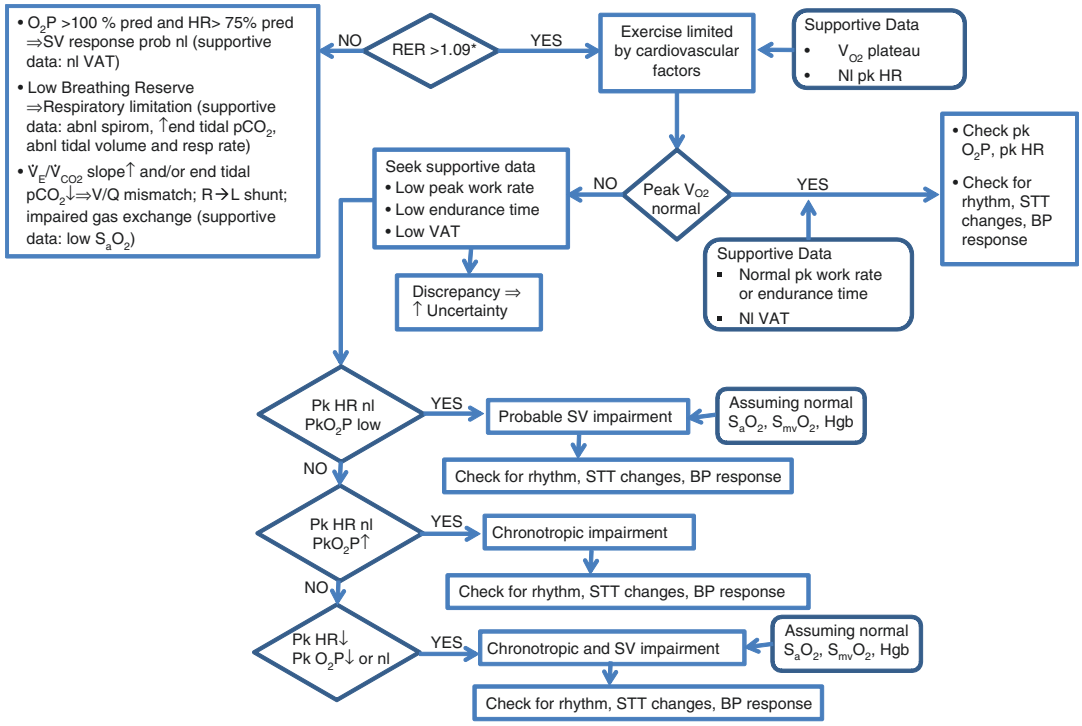
If one concludes that exercise was terminated on account of a cardiovascular limitation, one should then examine the peak V_{O2} and peak work rate (or, for treadmill exercise, the endurance time) data. If these data are normal, the patient's cardiovascular response to exercise is probably normal. It is also possible that the patient has a chronotropic defect with an excellent compensatory increase in the stroke volume response to exercise. Evaluation of the peak HR and peak O_2 pulse data will resolve this uncertainty. If there is a discrepancy between the peak $\dot{V}_{O2}$ and peak work rate data, one should consider possible causes for this discrepancy (e.g., malfunction of the gas analyzers, use of an inappropriate prediction equation, training effect, neurologic or orthopedic issue, etc.) and recognize that a significant discrepancy introduces an additional layer of uncertainty into the data analysis.

If the peak V_{O2} and peak work rate are low, one should look at the peak heart rate and peak O_2 pulse data. If the peak heart rate is normal, but the peak O_2 pulse is low, the patient probably has a

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_13



*$\dot{V}_E/\dot{V}_{CO2}$ slope, end tidal pCO_2, RR, tidal volume, breathing reserve and spirometry should also be assessed at the end of each branch point

Fig. 13.1 Algorithm for the assessment of cardiopulmonary exercise test data. Abbreviations: BP blood pressure, Hgb hemoglobin, HR heart rate, nl normal, O_2P oxygen pulse, pk peak, RER respiratory exchange ratio, S_aO_2 arterial oxygen saturation, $S_{mv}O_2$ mixed venous oxygen saturation, SV stroke volume, VAT ventilatory anaerobic threshold, $\dot{V}_{O2}$ oxygen consumption

depressed stroke volume response to exercise. This impression can be supported by observing an excessive heart rate response to exercise, manifested by a steeper-than-expected heart rate vs. $\dot{V}_{O2}$ curve. However, one should bear in mind the assumptions that underlie the typical close relationship between the oxygen pulse and stroke volume at peak exercise (i.e., that arterial oxygen saturation, mixed venous oxygen saturation, and hemoglobin levels are normal). One should therefore assess the pulse oximetry data and review the patient's clinical history and be prepared to adjust one's conclusions on the basis of this analysis. Among patients with congenital heart disease, a low arterial oxygen saturation is almost always due to right-to-left intracardiac or intrapulmonary shunting. Low arterial oxygen saturations can also be due to pulmonary venous desaturation secondary to pulmonary parenchymal abnormalities as may be seen in patients with atelectasis, pleural effusions, pulmonary edema, congestive heart failure, and other conditions with impaired gas transport across the alveolar–capillary membrane. Arterial desaturation secondary to pulmonary venous desaturation may also be encountered in patients with pulmonary vascular disease, due to the rapid red blood cell pulmonary capillary transit time encountered in that condition.

If the peak heart rate is low, a chronotropic defect is present. If a chronotropic defect is present, the stroke volume and oxygen pulse at peak exercise should be higher than normal, solely on the basis of the Starling effect. If the oxygen pulse at peak exercise is low or only "normal" (rather than supranormal), despite the presence of a low peak heart rate, a coexistent stroke volume impairment may be inferred.

Data from the ventilatory anaerobic threshold (VAT) should then be examined. The impression, based on the peak exercise data, that cardiovascular response to exercise is normal should be supported by the finding of a normal $\dot{V}_{O2}$ at the VAT. In contrast, one would expect to find a low $\dot{V}_{O2}$ at the VAT if the peak $\dot{V}_{O2}$ and peak work rate are depressed. However, it should be noted that the $\dot{V}_{O2}$ at the VAT may be relatively well preserved (compared to peak exercise parameters), especially in patients with congenital heart disease (CHD), because at submaximal exercise an enhanced chronotropic response can compensate for a stroke volume impairment and vice versa.

To complete the assessment of the cardiovascular response to exercise, the blood pressure response to exercise should then be reviewed and the electrocardiogram (EKG) recordings analyzed for the presence of rhythm disturbances and ST changes.

If the RER is ≤1.09, one may still be able to extract from the peak exercise data meaningful insights into a patient's cardiovascular function. Unless the heart rate at exercise termination is extremely low (e.g., <75% predicted, indicating the possible presence of a chronotropic impairment with a compensatory increase in stroke volume), a peak exercise O_2 pulse >100% predicted strongly suggests that the stroke volume response to exercise is normal, as it is unlikely that the O_2 pulse would be lower if an optimal effort had been expended. This impression would be supported by a normal $\dot{V}_{O2}$ at the VAT (if the VAT can be confidently identified), as this would signify that the cardiovascular system's ability to provide O_2 to the exercising muscles during submaximal exercise is intact.

Of course, the data acquired during a CPET study may also be affected by abnormalities of the respiratory system, which often coexist with the cardiovascular abnormalities encountered among patients with pediatric and congenital heart disease. Hence, attention should also be turned to data that reflect the lung function during exercise. The $\dot{V}_E/\dot{V}_{CO2}$ slope (which is valid even in the presence of a submaximal effort) should be determined to see if there is evidence of V/Q mismatch or other conditions that may impair gas exchange during exercise. The end-tidal pCO_2 curve should then be examined. A low end-tidal pCO_2 during exercise would support the conclusion that V/Q mismatch is present. CO_2 retention, reflected by an elevated end-tidal pCO_2 and/or an end-tidal pCO_2 that does not decline appropriately beyond the respiratory compensation point (in a test where an adequate effort is expended), indicates that significant respiratory disease is probably present. Abnormalities relating to the mechanics of the respiratory system should then be sought by examining the tidal volume and respiratory rate during exercise. A low tidal volume (relative to the baseline vital capacity) at peak exercise suggests air trapping; an elevated tidal volume (relative to baseline vital capacity) is suggestive of restrictive lung physiology. These impressions can be strengthened by data from pre- and (if available) postexercise spirometry and exercise flow-volume loops. An elevated respiratory rate at peak exercise may also indicate the presence of lung disease. Finally, the breathing reserve should be calculated to determine whether respiratory factors are contributing to or responsible for a patient's exercise limitation. Patients with a respiratory limitation typically have a low breathing reserve, abnormal lung mechanics, severe spirometric abnormalities, and (often) elevated end-tidal pCO_2, especially at higher levels of exercise. These patients may also have a low RER at peak exercise because they are unable to excrete the CO_2 produced even at low levels (i.e., below, or not much beyond, the VAT) of physical activity. They therefore do not develop a lactic acidosis and instead develop CO_2 retention and a respiratory acidosis, which forces them to terminate exercise before the RER rises above 1.09.

When the data from the CPET has been thoroughly analyzed, it should be compared to data from previous CPET studies. If significant time has elapsed (>6 months for children or adolescents; >3 years for adults) or if significant growth has occurred, it is usually best to compare %predicted values rather than absolute or weight-normalized values of $\dot{V}_{O2}$, work rate, O_2 pulse, and related parameters. This approach takes into account variations attributable solely to changes

in age, weight, or height and allows one to more readily recognize and appreciate changes related to alterations in cardiopulmonary function.

It is important to emphasize, once again, that CPET data must be interpreted within the context of the entire clinical picture. In patients with pediatric and congenital heart disease, CPET data rarely generates a specific diagnosis. Rather, it should be integrated with available information history, physical examination, imaging studies, electrophysiologic studies, pulmonary function testing, and laboratory and invasive studies to generate a comprehensive understanding of the patient's clinical status. In this regard, however, CPET data is often indispensable, as it is one of the only modalities that is capable of providing objective, quantifiable, and reproducible insights into a patient's exercise capacity and cardiopulmonary function during physical activities.

At this point in our discussion, it is appropriate to review the strengths and weaknesses of other methods that are commonly used to assess a patient's exercise function. A careful history is certainly an important and valuable component of any pediatric or congenital heart disease patient's evaluation and should 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 [2]. In a study of adolescents and young adults with CHD, Diller et al. [3] found 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 adult subjects nearly twice their age 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 al. [4] found that self-reported physical functioning was a poor predictor of 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 [2]. For instance, in the Pediatric Heart Network Fontan Study, the Child Health Questionnaire Physical Functioning Summary Score correlated poorly with results from formal exercise testing [5]. 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) [6].

The 6-minute walk test (6MWT) is easy to perform, does not require sophisticated equipment, mimics activities of daily living, and provides some information regarding a patient's exercise function [7]. 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 V_{O2} in highly symptomatic patients, its utility and validity in patients with "only" mild or moderate impairments is dubious [8]. Indeed, the reliability and meaning of the 6MWT for patients who can walk >400 m has been questioned [9]. 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 primary outcome variable (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 introduce considerable ambiguity into the

interpretation of an individual's test or even serial studies in a single individual. On account of these considerations, the utility of the 6MWT in children with CHD is limited. Finally, I also feel compelled to note that, 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 [6].

Exercise testing with EKG monitoring but without expiratory gas analysis is certainly useful in some settings (e.g., arrhythmias). However, it must be recognized that 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 EKG 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 [6].

For patients with all but the most simple (i.e., uncomplicated atrial septal defect, ventricular septal defect, or patent ductus arteriosus repairs) CHD lesions, it is reasonable to obtain a CPET study in late childhood/early adolescence, prior to participation in more formal and rigorous sports programs [10]. These studies can reassure the patient and/or parents, help identify important medical issues, and serve as useful baselines against which future studies can be compared. For patients with more complex defects, or those in whom there is a likelihood for problems to progress or evolve over time, serial testing at intervals of between 1 and 3 years (depending on clinical considerations) are reasonable. Concerning symptoms may be an indication for additional testing. Testing should also be considered before and after major medical, catheterization, or surgical interventions, to objectively characterize and quantify the results of the intervention.

References

1. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li J, et al. A cross-sectional study of exercise performance during the first two decades of life following the Fontan operation. J Am Coll Cardiol. 2008;52:99–107.
2. Rogers R, Reybrouck T, Weymans M, Dumoulin M, Van der HL, Gewillig M. Reliability of subjective estimates of exercise capacity after total repair of tetralogy of fallot. Acta Paediatr. 1994;83(8):866–9.
3. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation. 2005;112(6):828–35.
4. Gratz A, Hess J, Hager A. Self-estimated physical functioning poorly predicts actual exercise capacity in adolescents and adults with congenital heart disease. Eur Heart J. 2009;30(4):497–504.
5. Lambert LM, Minich LL, Newburger JW, Lu M, Pemberton VL, McGrath EA, et al. Parent- versus child-reported functional health status after the Fontan procedure. Pediatrics. 2009;124(5):e942–9.
6. Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.
7. Anonymous. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111–7.
8. Olsson LG, Swedberg K, Clark AL, Witte KK, Cleland JG. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. Eur Heart J. 2005;26(8):778–93.
9. Gratz A, Hess J, Hager A. Peak oxygen uptake and exercise capacity: a reliable predictor of quality of life? Reply. Eur Heart J. 2009;30:1674–5.
10. Van Hare GF, Ackerman MJ, Evangelista JK, Kovacs RJ, Myerburg RJ, Shafer KM, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 4: congenital heart disease: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2015;66(21):2372–84.

Part IV

Prototypical Lesions

Repaired Tetralogy of Fallot

14

Jonathan Rhodes, Alexander R. Opotowsky, and Mark E. Alexander

Basic Anatomy

The characteristic anatomy of anterior-superior displacement of the conal septum, resulting in a malalignment ventricular septal defect and a variable degree of subvalvar, valvar, and supravalvar pulmonary stenosis, is well known. Tetralogy of Fallot in fact represents a spectrum of diseases with multiple important anatomic variations. Furthermore, there have been substantial changes in surgical management in the 60 years that have elapsed since the initial anatomic repair in 1958. The details of the anatomy and management are needed to place any exercise result in context. Specific details that should be considered include (but are in no way limited to) age at complete repair, extent of an infundibulotomy or use of a conduit, prior shunts, and subsequent surgical and catheterization management.

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

A. R. Opotowsky
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Exercise Physiology Laboratory, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: alexander.opotowsky@cardio.chboston.org

M. E. Alexander
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Exercise Physiology, Arrhythmia Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: mark.alexander@cardio.chboston.org

Hemodynamics

The hemodynamics of patients with repaired tetralogy of Fallot (rTOF) is often characterized by an incompetent pulmonary valve and variable degrees of residual pulmonic stenoses at the subvalvar, valvar, supravalvar, branch, or peripheral pulmonary arterial levels. These anatomic abnormalities can affect the cardiopulmonary response to exercise and produce alterations in cardiopulmonary exercise testing (CPET) data that reflect interesting physiology with important clinical implications.

Exercise Capacity

Numerous studies have documented that the exercise capacity of patients with rTOF is often depressed. This is particularly notable in adults,

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_14

with younger cohorts often having $\dot{V}_{O2}$ max close to the normal range. In a study of 99 adults with rTOF, Samman et al. documented the %predicted peak $\dot{V}_{O2}$ to be depressed at 66 ± 13% of predicted [1]. In a larger single-center study of 168 adults with rTOF, Fredriksen et al. documented a peak $\dot{V}_{O2}$ of 51% predicted, with the lowest values in older patients and those with history of later surgical repair [2]. Diller et al. studied a cohort of 107 adults at a mean age of 32 years (with tetralogy of Fallot repair at a mean age of 6 years) and reported a mean peak $\dot{V}_{O2}$ of 56% predicted [3]. In a group of 377 adolescents and adults (age >14 years), Inuzuka found a median peak $\dot{V}_{O2}$ of 71% predicted, and only 25% had a peak $\dot{V}_{O2}$ >85% predicted [4]. In contrast, in a study of 50 children and adolescents (mean age at CPET 12.5 years; mean age at repair 11 months), Mahle et al. reported that although 16% of the patients had a peak $\dot{V}_{O2}$ <80% predicted, the overall peak $\dot{V}_{O2}$ averaged 95% predicted [5].

From these cross-sectional studies, there emerges a pattern of an age-related decrease in exercise function. This impression was confirmed by a longitudinal study that examined serial exercise tests in a group of 70 rTOF patients. Their initial peak $\dot{V}_{O2}$, at a mean age of 28 ± 15 years, averaged 78 ± 19% predicted [6]. Although there was great variability, an average decline in %predicted peak $\dot{V}_{O2}$ of 1.4 ± 9.2 percentage points per year was observed.

The factors responsible for the rTOF patient's exercise intolerance are probably diverse and may vary from patient to patient. In most cases, residual cardiovascular lesions (pulmonic stenosis, pulmonary regurgitation, ventricular dysfunction) are the most important issues [7–12]. The dynamic interaction between all of the variables that can affect the exercise function of these patients is complex, however, and can vary over time. As discussed as follows, pulmonary regurgitation, in particular, may be mitigated or exacerbated by other factors.

Moreover, chronic pulmonary regurgitation can have direct, deleterious effects upon ventricular function. In patients with significant pulmonary regurgitation, the right ventricle dilates in response to the regurgitant volume load imposed by the incompetent pulmonary valve [13]. In some of these patients, as the right ventricular volume increases, the wall thickness decreases and the right ventricular wall stress increases in accordance with the Law of Laplace. These developments, along with right ventricular hypertension related to residual pulmonary stenosis and/or abnormalities of the pulmonary vasculature, may ultimately culminate in right ventricular fibrosis and progressive, eventually irreversible, right ventricular dysfunction [14, 15]. The right ventricular dysfunction may also ultimately become associated with left ventricular dysfunction [16]. This phenomenon is thought to be due, at least in part, to altered right/left ventricular interaction [14]. The dilated, volume-overloaded right ventricle causes the ventricular septum to shift posteriorly (toward the LV) during diastole. This abnormal septal configuration can adversely affect both left ventricular filling (diastolic function) and left ventricular systolic function. In this context, left ventricular dysfunction is an ominous development that has been found to be associated with a poor clinical outcome [14, 17].

Arrhythmias in rTOF can be thought of as relatively simple circuit-based arrhythmias (typical atrial flutter and monomorphic VT). These arrhythmias are essentially an expected consequence of the surgical incisions that permit critical isthmuses of slow conduction. In addition, there are potentially more dangerous polymorphic ventricular arrhythmias and, particularly in the older patient, atrial fibrillation. Both are clinically important, with the distinction helping to clarify modern management [18, 19]. Hence, in any given patient, an integration of data from exercise testing, imaging studies, and other investigations is needed to accurately pinpoint the cause(s) of an rTOF patient's exercise intolerance.

In most cases, however, right ventricular function is the most important variable determining the rTOF patient's exercise function. In a

study of cardiac magnetic resonance imaging (MRI) correlates of exercise function in patients with rTOF, Meadows et al. reported that right ventricular ejection fraction was the only parameter independently related to peak $\dot{V}_{O2}$ [20]. Moreover, Kipps et al. reported that, in serial CPET studies, a time-related change in peak exercise oxygen pulse correlated strongly with a concomitant change in %predicted peak $\dot{V}_{O2}$ and accounted for more than 62% of the variability in this parameter [6]. This observation strongly suggests that a decline in the ability to augment forward stroke volume at peak exercise is responsible for the deterioration in exercise function that is commonly encountered among rTOF patients.

$\dot{V}_E/\dot{V}_{CO2}$ Slope

Several investigators have noted that patients with rTOF have inefficient gas exchange during exercise [8, 21, 22]. Clark et al. were the first to recognize that the $\dot{V}_E/\dot{V}_{CO2}$ slope is often elevated in patients with rTOF, especially those with a low peak $\dot{V}_{O2}$ [22]. The likely explanation for this phenomenon was proposed by Rhodes et al., on the basis of a study that both confirmed Clark's observation that there is a strong link between peak $\dot{V}_{O2}$ and the $\dot{V}_E/\dot{V}_{CO2}$ slope and also noted that the $\dot{V}_E/\dot{V}_{CO2}$ slope elevation is strongly correlated with pulmonary blood flow maldistribution detected on lung perfusion scans [23]. They proposed that the pulmonary blood flow maldistribution is due to pulmonary artery stenoses, which result in ventilation/perfusion mismatch, inefficient gas exchange, and elevation of the $\dot{V}_E/\dot{V}_{CO2}$ slope. The pulmonary artery stenoses also have a particularly deleterious effect upon the hemodynamics of patients with rTOF. As described in Chap. 4, exercise is normally associated with a marked decline in pulmonary vascular resistance due to a combination of pulmonary arteriolar vasodilation as well as the recruitment of pulmonary vascular beds that are normally unperfused or underperfused at rest. In patients with an incompetent pulmonary valve, this exercise-related decline in pulmonary vascular resistance would tend to promote forward blood flow, reduce regurgitation, and mitigate the hemodynamic impact of the valvular incompetence. However, in patients with pulmonary artery stenoses, the beneficial effects of the decline in pulmonary vascular resistance during exercise will be masked. As exercise intensity increases and cardiac output increases, the gradient across the fixed stenoses will increase. Pressure proximal to the stenoses will therefore rise. The main pulmonary artery hypertension and the obstruction to pulmonary artery blood flow caused by the pulmonary artery stenoses combine to exacerbate the severity of the pulmonary regurgitation; i.e., blood ejected by the right ventricle into the main pulmonary artery would be more likely to regurgitate back into the right ventricle. Hence, the pulmonary artery stenoses impose a progressive pressure and volume overload upon the right ventricle during exercise and may dramatically impair the ventricle's ability to increase cardiac output. The effective (forward) stroke volume will be low, and the patient will be unable to achieve a normal peak $\dot{V}_{O2}$ [23, 24].

Patients with pulmonary artery stenoses also tend to have low end-tidal pCO_2 during exercise. In the underperfused alveoli fed by the stenotic pulmonary arteries, pCO_2 levels over the course of each breath will not increase as much as they would in alveoli with normal perfusion. When air from the underperfused alveoli is exhaled, it mixes with the air from the normally perfused alveoli, dilutes the CO_2, and causes the end-tidal pCO_2 levels to decline.

Several subsequent studies have supported the understanding of the physiology described above. In a study of serial exercise tests performed in patients with rTOF before and after pulmonary artery balloon angioplasty procedures, Sutton et al. [24] found that those patients who had an improvement in their pulmonary blood flow maldistribution had improvements in their $\dot{V}_E/\dot{V}_{CO2}$ slope and their peak $\dot{V}_{O2}$ post-

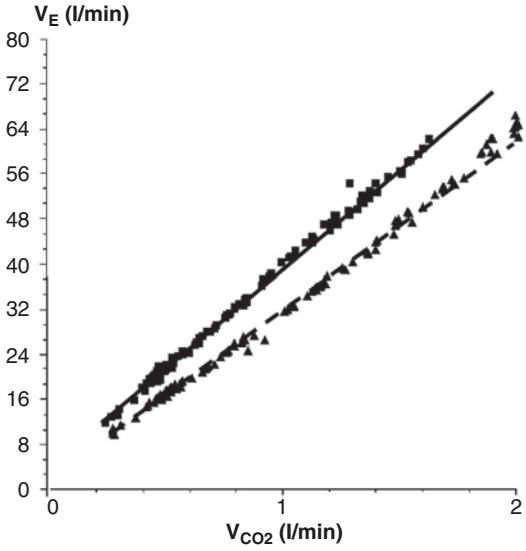


Fig. 14.1 Relationship between $\dot{V}_E$ and $\dot{V}_{CO2}$ in a patient with tetralogy of Fallot before and after successful pulmonary artery balloon angioplasty that increased left pulmonary artery blood flow from 13% to 35% of the total pulmonary blood flow. Square symbols are data points before angioplasty; triangular symbols are data points after angioplasty. The solid line represents the linear portion of the $\dot{V}_E/\dot{V}_{CO2}$ relationship before angioplasty (the slope of the line is the $\dot{V}_E/\dot{V}_{CO2}$ 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 $\dot{V}_{CO2}$. The $\dot{V}_E/\dot{V}_{CO2}$ slope fell from 35 to 29 and was associated with an increase in the peak $\dot{V}_{O2}$ from 18.8 to 23.7 mL/kg per minute and a rise in the end-tidal PCO_2 at the anaerobic threshold from 32 to 36 mm Hg. (Reprinted with permission from [25])

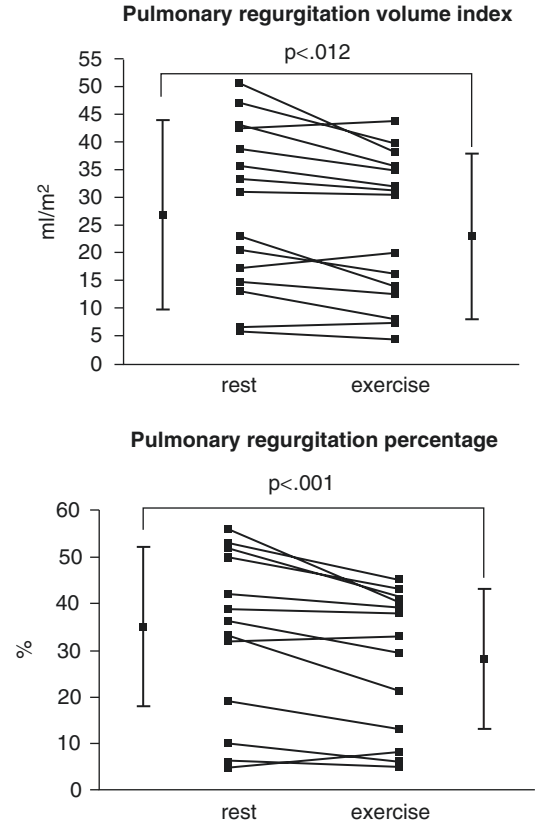


Fig. 14.2 Changes in pulmonary regurgitation (PR) volume index and PR percentage in response to supine physical exercise. Mean PR index and PR percentage significantly decreased from rest to exercise in patients with corrected tetralogy of Fallot. (Reprinted with permission from [26])

angioplasty (Fig. 14.1) [25]. In contrast, those who did not have a post-angioplasty improvement in pulmonary blood flow maldistribution had little change in their $\dot{V}_E/\dot{V}_{CO2}$ slope and peak $\dot{V}_{O2}$ post-angioplasty. In an exercise-MRI study, Roest et al. demonstrated that the pulmonary regurgitation volume and pulmonary regurgitation fraction of patients with rTOF decline with exercise (Fig. 14.2) [26]. Interestingly, Frigiola et al. reported that patients with rTOF who have not required pulmonary valve replacement did not have branch pulmonary artery stenosis and tended to have normal $\dot{V}_E/\dot{V}_{CO2}$ slopes and relatively well-preserved peak $\dot{V}_{O2}$ [27]. Finally, Harrild et al. [28] reported that patients who have undergone pulmonary valvuloplasty for isolated severe pulmonic stenosis tend to have normal or near-normal peak $\dot{V}_{O2}$ and $\dot{V}_E/\dot{V}_{CO2}$ slopes. These patients resemble rTOF patients in that they often have incompetent pulmonary valves. However, they rarely have peripheral pulmonary artery stenoses. Consequently, they rarely have pulmonary blood flow maldistribution and ventilation/perfusion mismatch, their $\dot{V}_E/\dot{V}_{CO2}$ slopes are normal, the hemodynamic impact of their incompetent valves is effectively mitigated by the exercise-related decline in pulmonary vascular resistance, and their ability to

increase their $\dot{V}_{O2}$ during exercise is well preserved.

It is also interesting to note that the time-related decline in %predicted peak $\dot{V}_{O2}$ that was detected in serial CPET studies performed on patients with rTOF correlated with a concomitant increase in the $\dot{V}_E/\dot{V}_{CO2}$ slope [6]. The factors responsible for the progressive elevation of the $\dot{V}_E/\dot{V}_{CO2}$ slope in these patients are probably varied and likely included pulmonary blood flow maldistribution and ventilation/perfusion mismatch secondary to pulmonary artery stenoses, pulmonary vascular disease, and/or congestive heart failure.

Other Abnormalities

Patients with repaired tetralogy of Fallot often have a depressed chronotropic response to exercise and will have subnormal peak exercise heart rates [29, 30]. Consequently, assessments of exercise function based on some obsolete, heart rate-based parameters, such as the work capacity at a heart rate of 170 bpm, may yield misleading conclusions – suggesting that the exercise capacity of rTOF patients is remarkably well preserved [7, 21, 30]. In fact, however, this conclusion may be based on a comparison of a rTOF patient near peak exercise (i.e., near his/her maximal heart rate) to a normal subject at submaximal exercise (e.g., at ~85% of peak heart rate).

Occasionally, patients with rTOF will develop right-to-left shunting across a patent foramen ovale or other atrial communication during exercise. This development reflects a disproportionate rise in right ventricular filling pressures as the right ventricle accommodates to the hemodynamic demands of exercise and probably indicates the presence of excessive residual hemodynamic lesions and/or right ventricular decompensation/failure. As one would expect based on the discussion of physiology presented in Chap. 12, this phenomenon is also accompanied by elevation of the $\dot{V}_E/\dot{V}_{CO2}$ slope and a decrease in end-tidal pCO_2 during exercise.

Spirometric Abnormalities

The forced vital capacity (FVC) and FEV1 of patients with rTOF are often depressed [8, 21]. This observation may be related to their history of cardiothoracic surgery or to underlying abnormalities of lung development [31]. Some investigators have detected a link between decreased lung volumes, increased pulmonary regurgitation, and depressed exercise function [8]. Patients with smaller lung volumes will tend to have more restrictive pulmonary vascular beds, and it is possible that physiology analogous to that described in patients with pulmonary artery stenosis may be operative in these cases.

Boston Children's Hospital Experience

Between 2003 and 2017, 2476 cardiopulmonary exercise tests were performed on 827 patients with tetralogy of Fallot at Boston Children's Hospital. Of these, 1892 were maximal as defined by a maximal respiratory exchange ratio >1.09. Age at the time of CPET averaged 30 ± 14 years old, and 47.7% of patients were female. Body mass index (BMI) averaged 24.7, and 17.3% of the patients were obese (BMI >30 kg/m^2). Most tests (78.1%) were performed by cycle ergometry with the rest performed using a treadmill. Description of exercise test results is provided in Table 14.1. On average, peak $\dot{V}_{O2}$ is mildly reduced, with borderline low O_2 pulse. $\dot{V}_E/\dot{V}_{CO2}$ slope is elevated >29 in about a quarter of patients. More than mild hypoxemia is rare. Peak $\dot{V}_{O2}$ indexed to body mass declines steadily with age, but relative to population normative values remains stable at ~70% predicted after the second decade; likewise, O_2 pulse remains ~80% predicted after a decline over the second decade of life (Fig. 14.3). Peak heart rate declines with age in proportion to expected age-related change.

In our review of arrhythmias during exercise tests performed at Boston Children's Hospital between 2013 and 2015, 372 of 555 patients

Table 14.1 Data from patients with repaired tetralogy of Fallot undergoing cardiopulmonary exercise tests at Boston Children's Hospital (2003–2017)

	n	Peak $\dot{V}_{O2}$ (% predicted)	Peak $\dot{V}_{O2}$ (mL/kg/min)	Peak HR (bpm)	Peak O_2 pulse (% predicted)	$\dot{V}_E / \dot{V}_{CO2}$ slope	Resting O_2 saturation (%)	Peak O_2 saturation (%)
All	1,892	72±16	25±8	159±24	82±19	28±5	98±2	96±3
		47-61-72-83-100	14-19-24-30-39	114-144-164-179-190	54-69-80-94-116	21-24-27-30-36	95-97-98-99-100	91-96-97-98-99
≤ 18 Years old	459	80±15	31±8	172±17	90±18	29±5	98±1	97±3
		53-70-80-91-105	19-26-31-36-44	140-162-176-184-194	59-76-89-102-119	23-25-28-31-38	97-98-99-99-100	91-97-98-98-99
19-30 Years old	640	70±16	26±6	165±21	78±17	27±5	98±2	97±3
		46-59-69-80-97	16-21-25-30-37	125-153-169-181-193	52-67-76-88-111	20-24-26-29-36	95-98-98-99-100	91-96-97-98-99
> 30 Years old	793	70±16	21±6	147±25	81±19	27±5	97±2	96±3
		46-59-68-80-98	12-17-21-25-32	102-130-150-166-182	53-67-79-91-116	21-24-27-30-36	95-97-98-98-99	90-95-97-98-99

Data are presented as mean ± SD with $^{5\text{-}25\text{-}50\text{-}75\text{-}95^{th}}$ percentiles in the row directly below
HR heart rate, *bpm* beats per minute

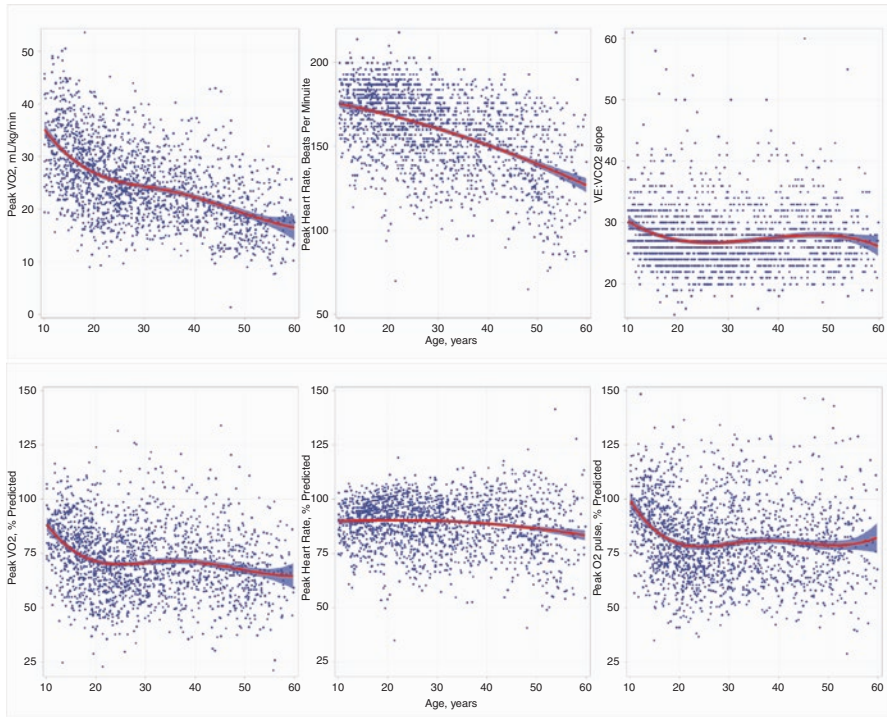


Fig. 14.3 Cardiopulmonary exercise test findings in patients with tetralogy of Fallot who completed a maximal (respiratory exchange ratio >1.09) exercise test at Boston Children's Hospital between 2003 and 2017 ($N = 1892$). Each point represents data for a single cardiopulmonary exercise test. The red line represents a restricted cubic spline fit to the data, with 95% confidence limits for the best-fit line in semitransparent blue. Only data for patients 10–60 years old with values between 20% and 150% predicted are presented

(67%) with TOF who underwent exercise stress test (EST) developed minor rhythm disturbances. However, only one required test termination on account of an arrhythmia (self-terminating, narrow complex tachycardia). No more serious arrhythmic events were encountered [32].

Pulmonary Valve Replacement

Pulmonary valve replacement has not been found to reliably improve the exercise capacity of patients with rTOF [33–39]. This unexpected finding is probably due, in part, to the exercise-related reduction in pulmonary regurgitation that occurs in the subset of patients undergoing valve replacement for isolated pulmonary regurgitation (a subset that comprises the majority of patients referred for pulmonary valve replacement). Since this physiologic phenomenon mitigates the hemodynamic effects of the incompetent pulmonary valve, it is not really surprising to find that implantation of a new pulmonary valve is not associated with the benefits that might have been predicted based on resting imaging and/or hemodynamic measurements. Studies have found, however, that the exercise function of the subset of patients with significant residual pulmonic stenosis [37, 38] and/or evidence of right ventricular dysfunction (e.g., low right ventricular ejection fraction or significant tricuspid insufficiency) does in fact improve following pulmonary valve implantation [39]. In contrast to pulmonary regurgitation, these hemodynamic lesions are not ameliorated by the decline in pulmonary vascular resistance during exercise. However, implantation of a well-functioning valve that relieves an obstruction and/or reduces the pressure/volume work of a failing right ventricle would be expected to have a salutary effect on exercise hemodynamics and exercise function.

The lack of improvement in peak $\dot{V}_{O2}$ in many patients following pulmonary valve replacement may also reflect the fact that peak $\dot{V}_{O2}$ is in fact determined, as we have seen, by a complex interaction between the cardiovascular system and the skeletal muscles [40]. Hence, interventions that improve the cardiovascular system may often have only a limited impact upon peak $\dot{V}_{O2}$ unless coupled with interventions that improve skeletal muscle function, and *vice versa*.

Prognostic Value of CPET Data in Tetralogy of Fallot

CPET data has been found to provide valuable prognostic information in patients with rTOF. Giardini et al. found that patients with $\dot{V}_E/\dot{V}_{CO2}$ slope >39 and those with peak $\dot{V}_{O2}$ <36% of predicted were at much greater risk for cardiac-related death (5-year mortality 48% vs 0%, p <0.0001, and 31% vs 0%, p <0.0001, respectively) [41]. Excellent prognostic power was also observed for cardiovascular hospitalization (Fig. 14.4) [41]. Similarly Buys et al. reported

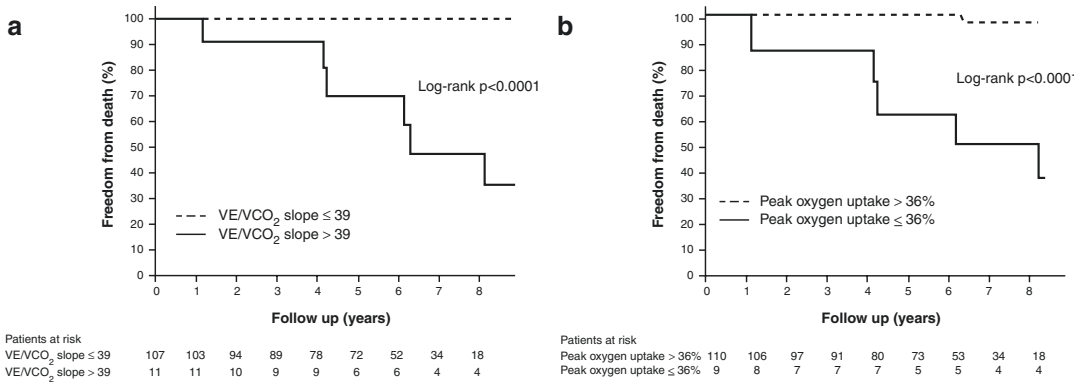


Fig. 14.4 Kaplan-Meier plots for the end points of death (**a**, **b**) and hospitalization (**c**, **d**) for $\dot{V}_E/\dot{V}_{CO2}$ slope (top) and %predicted peak $\dot{V}_{O2}$ (bottom). Patients were stratified using the cutoff values provided by receiver-operating characteristic curve analysis (Reprinted with permission from [41])

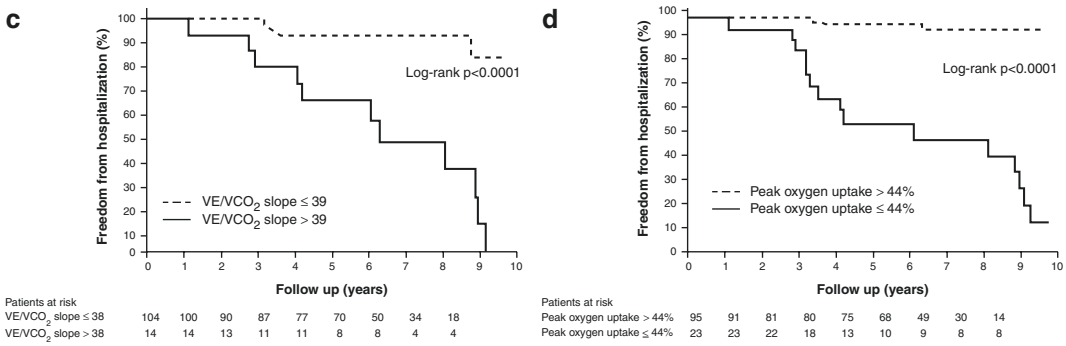


Fig. 14.4 (continued)

that %predicted peak $\dot{V}_{O2}$ and the $\dot{V}_E/\dot{V}_{CO2}$ slope were significantly related to the incidence of death/cardiovascular-related intervention [42]. More recently, Muller et al. reported that the peak $\dot{V}_{O2}$ and the $\dot{V}_E/\dot{V}_{CO2}$ slope independently predicted event-free survival [43].

Prototypical Patients

The first patient was a 26-year-old woman who underwent non-transannular repair of TOF when she was 11 months old. She did well following her surgery and remained asymptomatic. She was physically active and engaged in kickboxing and spin classes several days a week. Her echocardiogram revealed good RV and LV ventricular function, moderate RV dilation, and no significant RV outflow tract obstruction. There was moderate pulmonary regurgitation and trivial tricuspid regurgitation. No residual shunt lesions were detected. The exercise test (Table 14.2 and Fig. 14.5) was obtained to further characterize her cardiopulmonary status.

Based on her peak respiratory exchange ratio (RER) and peak heart rate, the patient expended a good effort. Her peak $\dot{V}_{O2}$ peak and work rate were normal. Her ability to increase her heart rate and forward stroke volume (as reflected by her excellent O_2 pulse at peak exercise) were normal. Her VAT was in the normal range, and her lungs appeared to exchange gas efficiently during exercise.

Table 14.2 Selected data from cardiopulmonary exercise test – patient 1

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	34.0
Peak $\dot{V}_{O2}$ (%predicted)	98
Peak work rate (W)	153
Peak work rate (%predicted)	117
Peak RER	1.18
Peak O_2 pulse (%predicted)	103
Peak heart rate (bpm)	171
Peak heart rate (%predicted)	96
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	66
Arterial oxygen saturation	Normal
Breathing reserve (%)	44
$\dot{V}_E/\dot{V}_{CO2}$ slope	27
End-tidal pCO_2 at VAT (mm Hg)	38
End-tidal pCO_2 during exercise	Normal
Spirometry	Normal
Blood pressure response	Normal

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

The well-preserved exercise function of this young woman, despite the presence of moderate pulmonary regurgitation and RV dilation, was probably the result of a healthy pulmonary vascular bed (reflected by the normal $\dot{V}_E/\dot{V}_{CO2}$ slope and end-tidal pCO_2 levels), which was able to effectively lower the pulmonary vascular resistance during exercise and thereby reduce the severity of the pulmonary regurgitation during exercise. Her regular exercise regimen also undoubtedly contributed to her excellent exercise function.

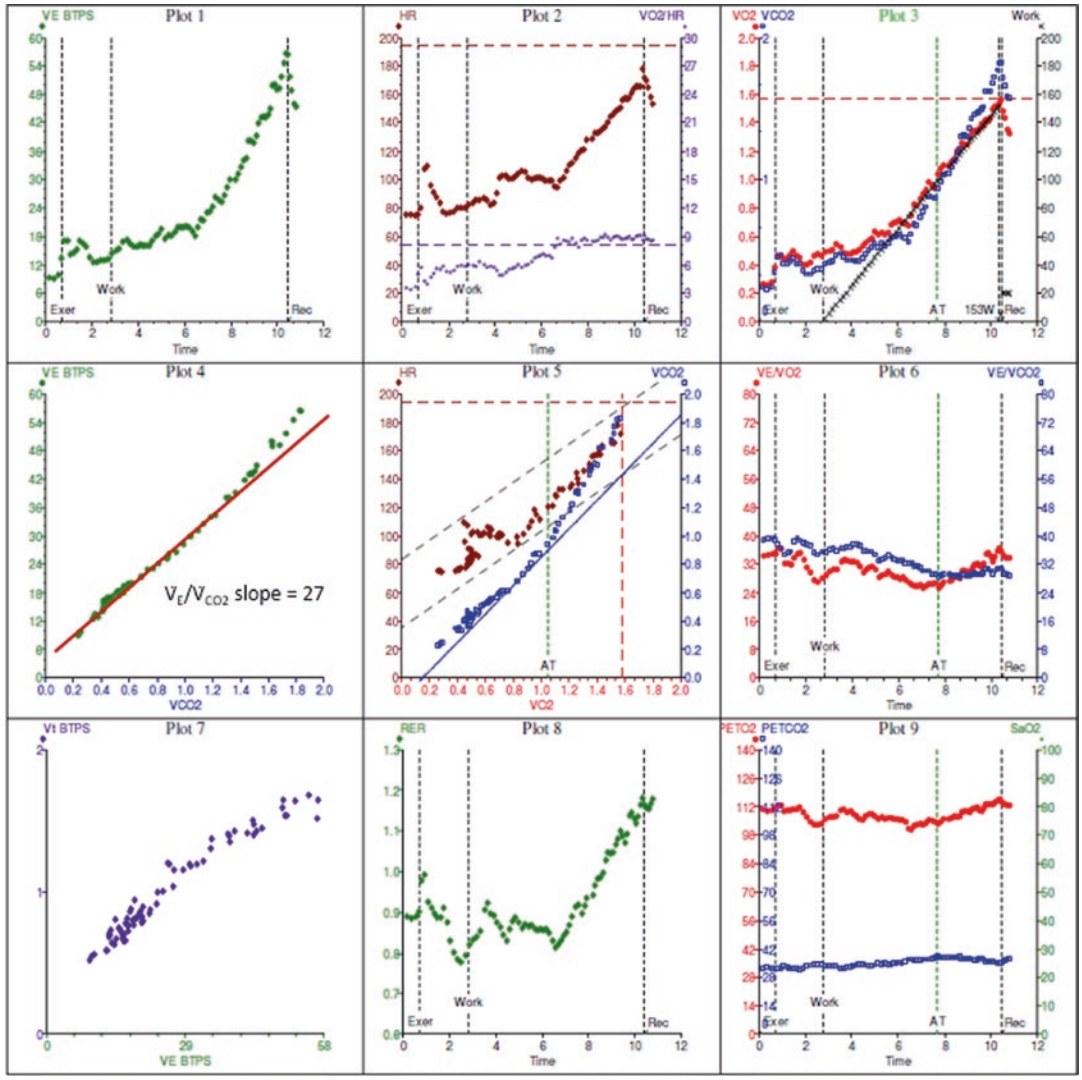


Fig. 14.5 Nine-panel graph of data from cardiopulmonary exercise test from patient 1. Abbreviations: AT ventilator anaerobic threshold; BTPS body temperature and pressure, saturated; Exer exercise; $PETCO_2$ end-tidal pCO_2; $PETO_2$ end-tidal pO_2; Rec recovery; RER respiratory exchange ratio; $\dot{V}_{CO2}$ carbon dioxide production; $\dot{V}_E$ minute ventilation; $\dot{V}_{O2}$ oxygen consumption; $\dot{V}_{O2}$/HR oxygen pulse

The second patient was a 20-year-old female who had a non-transannular repair of TOF when she was 9 months old. Following her surgery she was followed with a degree of pulmonary regurgitation and left pulmonary artery stenosis, which became progressively worse during childhood. When she was 7 years old, her left pulmonary artery was dilated and stented in the cardiac catheterization laboratory. The stent was re-dilated when she was 15 years old. Following this procedure, the left pulmonary artery perfusion increased from 16% to 36% of her total pulmonary blood flow.

At the time of her exercise test, she denied any cardiopulmonary symptoms. She did not engage in regular exercise, however. A cardiac MRI exam revealed mild RV dilation (RV end-diastolic volume 121 ml/m^2) with normal RV function

(RVEF 63%). There was moderate pulmonary regurgitation (PR fraction 31%). The left pulmonary artery arose acutely from the main pulmonary artery and received 33% of the total pulmonary blood flow. The LV function was normal. No residual shunts were detected. The exercise test was obtained (Table 14.3 and Fig. 14.6) to further characterize her cardiopulmonary status.

Based on her peak RER, the patient expended a good effort. Her peak $\dot{V}_{O2}$ peak and work rate were depressed. Her peak heart rate was low. Her forward stroke volume at peak, as reflected by her O_2 pulse, was probably in the low normal range. Her VAT was low. Her $\dot{V}_E/\dot{V}_{CO2}$ slope was elevated, and her end-tidal pCO_2 during exercise was low. Her spirometric measurements were normal.

Her diminished exercise capacity appeared due to a combination of a chronotropic defect as well as an inappropriately low stroke volume response to exercise. In the presence of a chronotropic defect, she should have had a compensatory increase in stroke volume (solely on the basis of the Starling mechanism). Hence, the fact that her forward stroke volume at peak exercise was only in the "low-normal" range was, in reality, quite abnormal. The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 during exercise were consistent with V/Q mismatch secondary to her known left artery stenosis and pulmonary blood flow maldistribution. It is likely that the pulmonary artery stenosis obstructed blood flow to the left lung during exercise, blocked the hemodynamically beneficial effects of the exercise-related decline in pulmonary vascular resistance, caused the pressure proximal to the obstruction to rise excessively, exacerbated the pulmonary regurgitation, and imposed a progressive pressure and volume load upon the RV. Consequently the RV could neither compensate for the chronotropic defect nor support the hemodynamic demands of exercise.

Table 14.3 Selected data from cardiopulmonary exercise test – patient 2

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	23.9
Peak $\dot{V}_{O2}$ (%predicted)	66
Peak work rate (W)	123
Peak work rate (%predicted)	77
Peak RER	1.12
Peak O_2 pulse (%predicted)	87
Peak heart rate (bpm)	141
Peak heart rate (%predicted)	76
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	39
Arterial oxygen saturation	Normal
Breathing reserve (%)	62
$\dot{V}_E/\dot{V}_{CO2}$ slope	32
End-tidal pCO_2 at VAT (mm Hg)	33
End-tidal pCO_2 during exercise	Low
Spirometry	Normal
Blood pressure response	Normal

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

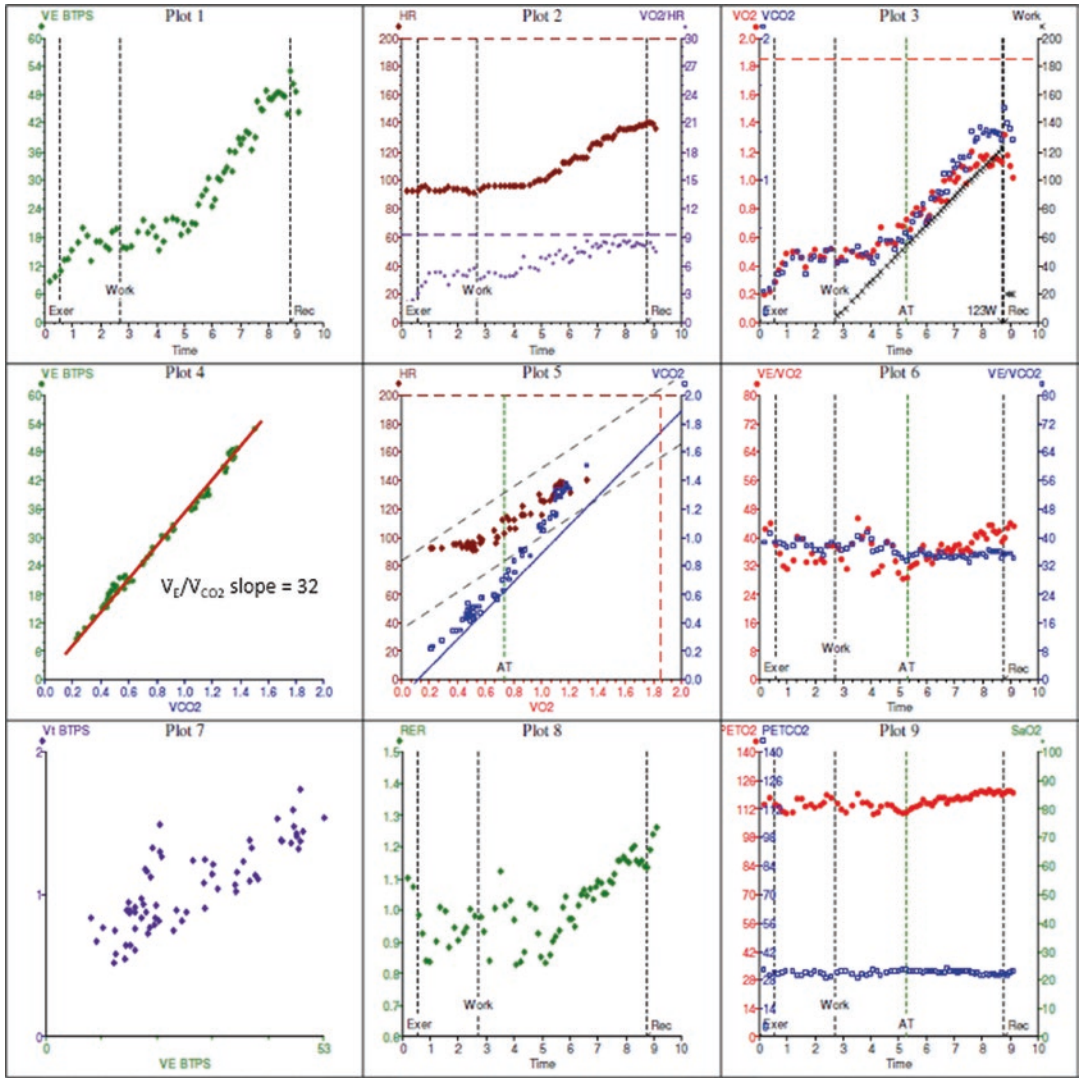


Fig. 14.6 Nine-panel graph of data from cardiopulmonary exercise test from patient 2. Abbreviations: AT ventilator anaerobic threshold; BTPS body temperature and pressure, saturated; Exer exercise; $PETCO_2$ end-tidal pCO_2; $PETO_2$ end-tidal pO_2; Rec recovery; RER respiratory exchange ratio; $\dot{V}_{CO2}$ carbon dioxide production; $\dot{V}_E$ minute ventilation; $\dot{V}_{O2}$ oxygen consumption; $\dot{V}_{O2}$/HR oxygen pulse

References

1. Samman A, Schwerzmann M, Balint OH, Tanous D, Redington A, Granton J, et al. Exercise capacity and biventricular function in adult patients with repaired tetralogy of Fallot. Am Heart J. 2008;156(1):100–5.
2. Fredriksen PM, Therrien J, Veldtman G, Ali WM, Liu P, Thaulow E, et al. Aerobic capacity in adults with tetralogy of Fallot. Cardiol Young. 2002;12(6):554–9.
3. Diller GP, Dimopoulos K, Okonko D, Uebing A, Broberg CS, Babu-Narayan S, et al. Heart rate response during exercise predicts survival in adults with congenital heart disease. J Am Coll Cardiol. 2006;48(6):1250–6.
4. Inuzuka R, Diller GP, Borgia F, Benson L, Tay ELW, Alonso-Gonzalez R, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation. 2012;125(2):250–9.
5. Mahle WT, McBride MG, Paridon SM. Exercise performance in tetralogy of Fallot: the impact of primary complete repair in infancy. Pediatr Cardiol. 2002;23(2):224–9.
6. Kipps AK, Graham DA, Harrild DM, Lewis E, Powell AJ, Rhodes J. Longitudinal exercise capacity of patients with repaired tetralogy of Fallot. Am J Cardiol. 2011;108(1):99–105.
7. Wessel HU, Cunningham WJ, Paul MH, Bastanier CK, Muster AJ, Idriss FS. Exercise performance in tetralogy of Fallot after intracardiac repair. J Thorac Cardiovasc Surg. 1980;80(4):582–93.
8. Rowe SA, Zahka KG, Manolio TA, Horneffer PJ, Kidd L. Lung function and pulmonary regurgitation limit exercise capacity in postoperative tetralogy of Fallot. J Am Coll Cardiol. 1991;17(2):461–6.
9. Dallaire F, Wald RM, Marelli A. The role of cardiopulmonary exercise testing for decision making in patients with repaired tetralogy of Fallot. Pediatr Cardiol. 2017;38(6):1097–105.
10. Buys R, Cornelissen V, Van De Bruaene A, Stevens A, Coeckelberghs E, Onkelinx S, et al. Measures of exercise capacity in adults with congenital heart disease. Int J Cardiol. 2011;153(1):26–30.
11. Eyskens B, Brown SC, Claus P, Dymarkowski S, Gewillig M, Bogaert J, et al. The influence of pulmonary regurgitation on regional right ventricular function in children after surgical repair of tetralogy of Fallot. Eur J Echocardiogr. 2010;11(4):341–5.
12. Marx GR, Hicks RW, Allen HD, Goldberg SJ. Noninvasive assessment of hemodynamic responses to exercise in pulmonary regurgitation after operations to correct pulmonary outflow obstruction. Am J Cardiol. 1988;61:595–601.
13. Graham TP Jr, Cordell D, Atwood GF, Boucek RJ Jr, Boerth RC, Bender HW, et al. Right ventricular volume characteristics before and after palliative and reparative operation in tetralogy of Fallot. Circulation. 1976;54:417–23.
14. Schamberger MS, Hurwitz RA. Course of right and left ventricular function in patients with pulmonary insufficiency after repair of tetralogy of Fallot. Pediatr Cardiol. 2000;21(3):244–8.
15. Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG, Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? J Am Coll Cardiol. 2000;36:1670–5.
16. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol. 2004;43(1068):1074.
17. Ghai A, Silversides C, Harris L, Webb GD, Siu SC, Therrien J. Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot. J Am Coll Cardiol. 2002;40(9):1675–80.
18. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet. 2000;356(9234):975–81.
19. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation. 1995;92:231–7.
20. Meadows J, Powell AJ, Geva T, Dorfman A, Gauvreau K, Rhodes J. Cardiac magnetic resonance imaging correlates of exercise capacity in patients with surgically repaired tetralogy of Fallot. Am J Cardiol. 2007;100(9):1446–50.
21. Strieder DJ, Aziz K, Zaver AG, Fellows KE. Exercise tolerance after repair of tetralogy of Fallot. Ann Thorac Surg. 1975;19(4):397–405.
22. Clark AL, Gatzoulis MA, Redington AN. Ventilatory responses to exercise in adults after repair of tetralogy of Fallot. Br Heart J. 1995;73(5):445–9.
23. Rhodes J, Dave A, Pulling MC, Geggel RL, Marx GR, Fulton DR, et al. Effect of pulmonary artery stenoses on the cardiopulmonary response to exercise following repair of tetralogy of Fallot. Am J Cardiol. 1998;81(10):1217–9.
24. Sutton NJ, Peng L, Lock JE, Lang P, Marx GR, Curran TJ, et al. Effect of pulmonary artery angioplasty on exercise function after repair of tetralogy of Fallot. Am Heart J. 2008;155(1):182–6.
25. Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.
26. Roest AAW, Helbing WA, Kunz P, van den Aardweg JG, Lamb HJ, Vliegen HW, et al. Exercise MR imaging in the assessment of pulmonary regurgitation and

biventricular function in patients after tetralogy of Fallot repair. Radiology. 2002;223:204–11.
27. Frigiola A, Hughes M, Turner M, Taylor A, Marek J, Giardini A, et al. Physiological and phenotypic characteristics of late survivors of tetralogy of Fallot repair who are free from pulmonary valve replacement. Circulation. 2013;128(17):1861–8.
28. Harrild DM, Powell AJ, Trang TX, Geva T, Lock JE, Rhodes J, et al. Long-term pulmonary regurgitation following balloon valvuloplasty for pulmonary stenosis: risk factors and relationship to exercise capacity and ventricular volume and function. J Am Coll Cardiol. 2010;55(10):1041–7.
29. Takahashi O, Futaki S, Kamiya T. Exercise capacity of patients with post-operative tetralogy of Fallot. Jpn Circ J. 1986;50(9):863–4.
30. Reybrouck T, Weymans M, Stijns H, Van der Hauwaert LG. Exercise testing after correction of tetralogy of Fallot: the fallacy of a reduced heart rate response. Am Heart J. 1986;112(5):998–1003.
31. Rabinovitch M, Herrera-deLeon V, Castaneda AR, Reid L. Growth and development of the pulmonary vascular bed in patients with tetralogy of Fallot with or without pulmonary atresia. Circulation. 1981;64(6):1234–49.
32. Barry OM, Gauvreau K, Rhodes J, Reichman JR, Bourette L, Curran T, O'Neill J, Pymm JL, Alexander ME. Incidence and predictors of clinically important and dangerous arrhythmias during exercise tests in pediatric and congenital heart disease patients. JACC Clin Electrophysiol. 2018;4(10):1319–27.
33. Frigiola A, Tsang V, Bull C, Coats L, Khambadkone S, Derrick G, et al. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? Circulation. 2008;118(14 Suppl):S182–90.
34. Geva T, Gauvreau K, Powell AJ, Cecchin F, Rhodes J, Geva J, et al. Randomized trial of pulmonary valve replacement with and without right ventricular remodeling surgery. Circulation. 2010;122(11 Suppl):S201–8.
35. Ghez O, Tsang VT, Frigiola A, Coats L, Taylor A, van DC, et al. Right ventricular outflow tract reconstruction for pulmonary regurgitation after repair of tetralogy of Fallot. Preliminary results. Eur J Cardiothorac Surg. 2007;31(4):654–8.
36. Warner KG, O'Brien PK, Rhodes J, Kaur A, Robinson DA, Payne DD. Expanding the indications for pulmonary valve replacement after repair of tetralogy of Fallot. Ann Thorac Surg. 2003;76:1066–72.
37. Lurz P, Giardini A, Taylor AM, Nordmeyer J, Muthurangu V, Odendaal D, et al. Effect of altering pathologic right ventricular loading conditions by percutaneous pulmonary valve implantation on exercise capacity. Am J Cardiol. 2010;105(5):721–6.
38. Lurz P, Nordmeyer J, Giardini A, Khambadkone S, Muthurangu V, Schievano S, et al. Early versus late functional outcome after successful percutaneous pulmonary valve implantation: are the acute effects of altered right ventricular loading all we can expect? J Am Coll Cardiol. 2011;57(6):724–31.
39. Batra AS, McElhinney DB, Wang W, Zakheim R, Garofano RP, Daniels C, et al. Cardiopulmonary exercise function among patients undergoing transcatheter pulmonary valve implantation in the us melody valve investigational trial. Am Heart J. 2012;163(2):280–7.
40. Jones NL. Clinical exercise testing. 4th ed. Philadelphia: W. B. Saunders; 1997. p. 44–5.
41. Giardini A, Specchia S, Tacy TA, Coutsoumbas G, Gargiulo G, Donti A, et al. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of Fallot. Am J Cardiol. 2007;99:1462–7.
42. Buys R, Van De Bruaene A, De Meester P, Budts W, Vanhees L. Predictors of mid-term event-free survival in adults with corrected tetralogy of Fallot. Acta Cardiol. 2012;67(4):415–21.
43. Muller J, Hager A, Diller GP, Derrick G, Buys R, Dubowy KO, et al. Peak oxygen uptake, ventilatory efficiency and QRS-duration predict event free survival in patients late after surgical repair of tetralogy of Fallot. Int J Cardiol. 2015;196:158–64.

Fontan Circulation

15

Jonathan Rhodes and Alexander R. Opotowsky

Basic Anatomy

The Fontan procedure was initially suggested as a treatment for patients with tricuspid atresia [1, 2]. Since its introduction, the application of this innovative surgical approach has expanded to include patients with single-ventricle physiology secondary to a variety of anatomic disorders including hypoplastic left heart syndrome, double inlet or other single left ventricle, pulmonary atresia with intact ventricular septum, unbalanced atrioventricular septal defects, complex heterotaxy syndromes, and others. There has also been extensive evolution of the surgical approach. Currently two types of total cavopulmonary anastomoses, the lateral tunnel and extracardiac conduit modifications, are the most commonly employed modifications, as they appear to reduce the energy loss within the Fontan circuit and reduce the long-term risk of arrhythmias. Older patients with historic anatomic Fontan modifications including right atrial to pulmonary artery or right atrial to right ventricular anastomoses, with or without interposed valves within the Fontan circuit, are still encountered [3].

Exercise Hemodynamics

Patients with Fontan physiology are characterized by the absence of a sub-pulmonary ventricle; the pulmonary circulation is perfused passively by systemic venous pressure with variable support by the skeletal muscle venous pump [4–6]. Cardiac output and stroke volume, when measured in the catheterization laboratory or via non-invasive techniques, tend to be low-normal at rest, and there is a reduced exercise-related increase compared to patients with biventricular circulations [7–14]. Indeed, supine exercise-cardiac magnetic resonance imaging (MRI) [14] and exercise-echocardiographic [15] studies have reported that the stroke volume may sometimes decline during exercise due primarily to a decline in ventricular preload and end diastolic volume. Other studies have corroborated or indirectly

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

A. R. Opotowsky
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Exercise Physiology Laboratory, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: alexander.opotowsky@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_15

supported this observation. Invasive studies have demonstrated that, in contrast to patients with biventricular circulations and patients with Blalock-Taussig shunt-dependent circulations, the ventricular end diastolic pressure of Fontan patients often falls in response to dobutamine administration, in association with a more modest increase in systemic cardiac output [16]. Similar observations have been made with dobutamine stress echocardiography [17] and cardiac MRI [18–20]. In an elegant study that combined echocardiographic and invasive catheterization measurements (ventricular pressure-area hybrid loops) in response to inflow occlusion, atrial pacing and dobutamine administration, Senzaki et al. found that the cardiac output of Fontan patients is primarily dependent upon preload (as measured by end-diastolic area) rather than contractility or afterload [21]. Systemic ventricular preload could be limited by several factors including increased systemic venous capacitance [22], Fontan pathway obstruction, increased pulmonary vascular resistance [8, 9], or decreased systemic ventricular compliance [6, 9].

Among Fontan patients, oxygen delivery during exercise can be increased by other mechanisms, aside from an increase in stroke volume. For example, oxygen extraction is typically enhanced compared with the normal circulation for any given level of cardiac output [4, 11, 13, 23]. Although peak exercise heart rates tend to be lower than normal, the heart rate tends to be higher than normal for any given $\dot{V}_{O2}$ [11, 24].

Exercise Capacity

Exercise capacity is almost always depressed in patients with a Fontan circulation. In the Pediatric Heart Network Cross-Sectional Fontan study, the average peak $\dot{V}_{O2}$ of 166 pediatric patients who completed a clearly maximal effort exercise test (peak respiratory exchange ratio >1.09) was only 65% of predicted [25]. Another study found that the median peak $\dot{V}_{O2}$ of 92 adolescents and young adults with Fontan circulations was only 56% predicted and none had a peak $\dot{V}_{O2}$ > 90% predicted [26]. Other studies have yielded similar results [27–32].

Other Abnormalities

Fontan patients often have an elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 levels [30, 33]. These phenomena are usually due to: (1) V/Q mismatch secondary to the pulmonary blood flow maldistribution that results from the absence of normal pulmonary artery pulsatility in the passively perfused pulmonary vascular bed, and (2) residual right-to-left shunts. Alternative mechanisms, such as parenchymal lung disease or pulmonary arteriovenous malformations (AVM), can also coexist.

The forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) of Fontan patients are often depressed, usually in proportion (i.e., restrictive rather than obstructive spirometry pattern) [34]. A low FVC has been found to be independently associated with a lower peak $\dot{V}_{O2}$ [34]. One potential explanation for this phenomenon may be that the low FVC indicates the presence of smaller-than-normal lungs (either on the basis of congenital developmental issues or complications from cardiothoracic surgery and/or other traumatic events that may impair the growth and development of the lungs) and hence a more restrictive pulmonary vascular bed—a condition that would be particularly deleterious to the Fontan patient's cardiopulmonary response to exercise [4]. There is also an increased prevalence of chest wall deformity due to kyphoscoliosis or prior surgeries.

Natural History of Exercise Function in Fontan Patients

Serial exercise studies have found that the peak $\dot{V}_{O2}$ of Fontan patients tends to decline (relative to normal subjects) over time [31, 33, 35]. The decline appears to be steepest during the adolescent years, especially among adolescent males, and more gradual thereafter. These observations are probably related to the fact that normal male puberty is associated with a dramatic increase in skeletal muscle mass. It appears that the Fontan circulation is often incapable of meeting the metabolic demands of this increased muscle mass during exercise. In addition, muscle mass and strength tend to be lower in Fontan

patients compared to normal subjects [36]. The more gradual decline in peak $\dot{V}_{O2}$ during the adult years is probably related to age-related increases in pulmonary vascular resistance and/or ventricular filling pressure (secondary to a decline in ventricular compliance) [6]. Data from cross-sectional studies also support these generalizations [25, 27]. Once again, it should be emphasized that longitudinal changes in exercise function, relative to normal subjects, are best appreciated by analyzing changes in %predicted peak $\dot{V}_{O2}$ (rather than absolute or weight-normalized values), as the prediction equations take into account the expected increase in peak $\dot{V}_{O2}$ that is associated with growth during the pediatric years, as well as the age-related decline in peak $\dot{V}_{O2}$ that occurs in adulthood. For instance, the adolescent Fontan patient's decline in peak $\dot{V}_{O2}$, relative to normal individuals is not indicative of a decline in absolute peak $\dot{V}_{O2}$ (in ml/min), but rather a less robust increase relative to normal adolescent. Conversely, there is a real, albeit slow decline in absolute $\dot{V}_{O2}$ in young adulthood, but this decline is only slightly more prominent than that observed in normal individuals in the third decade of life. Finally, all of these changes occur on a backdrop of a lower baseline exercise capacity and, therefore, lower cardiopulmonary reserve.

Boston Children's Hospital Experience

Between January 2003 and December 2017, 1473 cardiopulmonary exercise tests (CPETs) were performed at Boston Children's Hospital on 450 patients who had a prior Fontan procedure. Of these tests, 1110 were maximal as defined by a peak respiratory exchange ratio >1.09. Among patients with maximal tests, age at the time of CPET averaged 22.9 ± 10.1 years, 37% were female, and body mass index (BMI averaged 23.0 ± 4.6 kg/m^2 with 9.1% obese (BMI >30 kg/m^2)). Most (85.6%) were performed by cycle ergometry rather than with treadmill. A description of exercise test results is provided in Table 15.1 and Fig. 15.1. In the single ventricle

Table 15.1 Boston Children's Hospital experience with Fontan patients who have had cardiopulmonary exercise tests (2003–2017)

	n	Peak $\dot{V}_{O2}$ (% predicted)	Peak $\dot{V}_{O2}$ (mL/kg/min)	Peak HR (bpm)	Peak O_2 Pulse (% predicted)	$\dot{V}_E/\dot{V}_{CO2}$ slope	Resting O_2 saturation (%)	Peak O_2 saturation (%)
All	1,110	63±15	24±7	149±25	79±19	33±7	92±4	89±6
		40-52-62-73-89	13-19-23-28-36	103-133-153-169-184	50-66-77-90-112	25-29-32-37-46	85-90-93-95-98	80-86-90-93-96
≤ 18 Years old	429	69±16	28±6	160±21	83±19	35±6	93±4	89±5
		45-58-68-79-95	18-23-28-32-38	116-150-164-174-187	55-69-82-95-117	26-30-34-38-46	85-91-94-96-98	79-87-91-93-96
19-30 Years old	449	61±14	23±5	147±23	77±17	33±6	92±4	88±5
		40-51-60-69-83	15-19-23-27-32	106-133-150-164-179	52-65-75-88-107	24-29-31-35-44	85-90-92-94-98	81-85-89-92-96
> 30 Years old	232	57±14	18±5	134±26	74±19	33±7	92±5	89±7
		34-47-56-66-85	10-15-18-21-28	92-116-133-150-174	45-59-76-86-106	23-28-32-36-46	83-91-93-95-97	80-88-90-93-96

Data are presented as mean ± SD with 5-25-50-75-95th percentiles in the row directly below
HR heart rate, *bpm* beats per minute

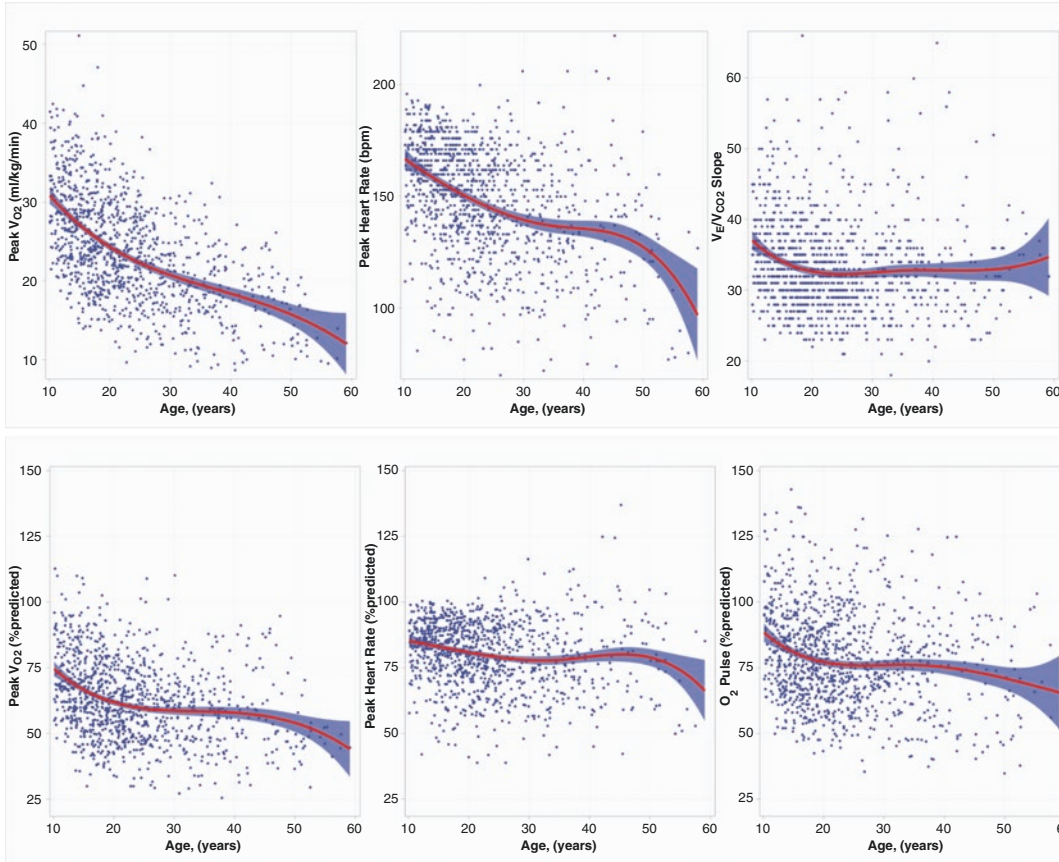


Fig. 15.1 Data from 1110 cardiopulmonary exercise test findings in 450 patients with Fontan circulations who completed a maximal (respiratory exchange ratio >1.09) exercise test at Boston Children's Hospital between 2003 and 2017. Each point represents data for a single cardiopulmonary exercise test. The red line represents a restricted cubic spline fit to the data, with 95% confidence limits for the best fit line in semitransparent blue

Fontan circulation, peak $\dot{V}_{O2}$ is almost universally depressed compared with predicted values (only 5% of patients tested are ≥89% predicted), and $\dot{V}_E/\dot{V}_{CO2}$ slope is elevated in about 75% of patients. Mild hypoxemia is the norm. With increasing age, peak $\dot{V}_{O2}$ declines both as ml/kg/min and compared to predicted values. This decline in peak $\dot{V}_{O2}$ is steepest before age 20 years and then becomes more gradual, paralleling the pattern for O_2 pulse. Peak heart rate is slightly lower than normal for age, and remains relatively stable compared to age-expected values across the age groups. The $\dot{V}_E/\dot{V}_{CO2}$ slope is elevated compared to normal, without a notable age-related change.

Exercise testing appears to be a very low risk undertaking in patients with Fontan circulations. In our review of arrhythmias during exercise tests performed at Boston Children's Hospital between 2013 and 2016, 437 tests were performed on patients who had Fontan procedures. Although low-grade ectopy was common (58% of studies), only 2 patients developed a supraventricular tachyarrhythmia that required test termination. In both cases, the patients remained stable and the arrhythmia resolved shortly after the termination of the study; no other interventions were required. No more complex ectopy was encountered.

Causes of Exercise Limitation in Fontan Patients

In any given patient, the cause(s) of the depressed exercise function may vary and may include: an

inability to increase stroke volume normally in response to exercise, chronotropic incompetence, arterial desaturation, pulmonary abnormalities, and deconditioning. Of these, the inability to increase the stroke volume is by far the most important. In the Pediatric Heart Network Fontan study, variations in the oxygen pulse accounted for 73% of the observed variation in peak V_{O2} and 26% of the variation (the mathematically unrelated) %predicted peak work rate, respectively. In contrast, variations in chronotropic index and resting arterial oxygen saturation accounted for no more than 3% of the variation in peak V_{O2} or peak work rate [25].

Cardiac Function

Ventricular dysfunction (both systolic and diastolic) is common among Fontan patients. This may result from the congenital malformation itself (e.g., a right ventricle serving as a systemic ventricle) as well as other stressors associated with single ventricle palliation. Prior to Fontan conversion (at least until the bidirectional Glenn stage), the ventricle is volume overloaded and must function in a hypoxemic environment. Following Fontan conversion, the ventricle is preload deprived and also must perform more work than the normal left ventricle in a biventricular circulation (see Fig. 15.2a, b). These factors often result in adverse ventricular remodeling [37]. Myocardial injury during the multiple surgical and catheterization procedures associated with Fontan palliation also may contribute to ventricular dysfunction.

Paradoxically, however, peak V_{O2} was not associated with any of the numerous echocardiographic parameters of ventricular function evaluated in the Pediatric Heart Network Fontan Study, including ventricular end-diastolic volume, ventricular end-systolic volume, stroke volume, ejection fraction, ventricular mass, mass/volume ratio, atrioventricular valve regurgitation, diastolic function, tissue Doppler indices, the mean dP/dt during isovolumetric contraction or the Tei index. Indeed, except for a weak, but statistically significant correlation between oxygen pulse at peak exercise and the mean dP/dt during isovolumetric contraction, there was no correlation between any echocardiographic index of ventricular function and any index of exercise function [25]. This implies that Fontan circulation's inability to augment stroke volume normally during exercise does not usually stem from abnormalities of ventricular or valvular function. More likely, an inability of the passively perfused pulmonary vascular bed to accommodate the increased blood flow required for exercise is often the factor that limits the Fontan patient's stroke volume response to exercise and consequently, his/her exercise capacity (Fig. 15.3a, b). Further supporting this concept are data that suggest the ventricular filling pressure and/or end diastolic volume of Fontan patients is reduced during exercise, implying that ventricular preload is reduced secondary to an inability to deliver blood through their passively perfused lungs [14–20]. In the absence of a fenestration (or analogous communication), the Fontan patient's ventricle can only pump blood that makes it through the lungs!

When severe, ventricular or valvular dysfunction can certainly adversely affect a Fontan patient's ability to exercise [37]. However, the poor correlation between exercise capacity and indices of ventricular and valvular function implies that the "weak link" for most Fontan patients usually resides elsewhere, e.g., in the pulmonary vascular bed [6] or, less commonly, in the sinus node/conduction system, rather than the myocardium or cardiac valves.

The Pulmonary Vascular Bed

The pulmonary vascular bed has therefore been identified as a potential therapeutic target in the Fontan circulation [37, 38]. Although patients are not selected for Fontan palliation unless their resting pulmonary vascular resistance is relatively low, the ability of the pulmonary vascular bed to dilate and recruit blood vessels, and thereby lower pulmonary vascular resistance during exercise (as described in Sect. 1 of this book) is almost never assessed prior to Fontan surgery. Furthermore, a number of studies have raised

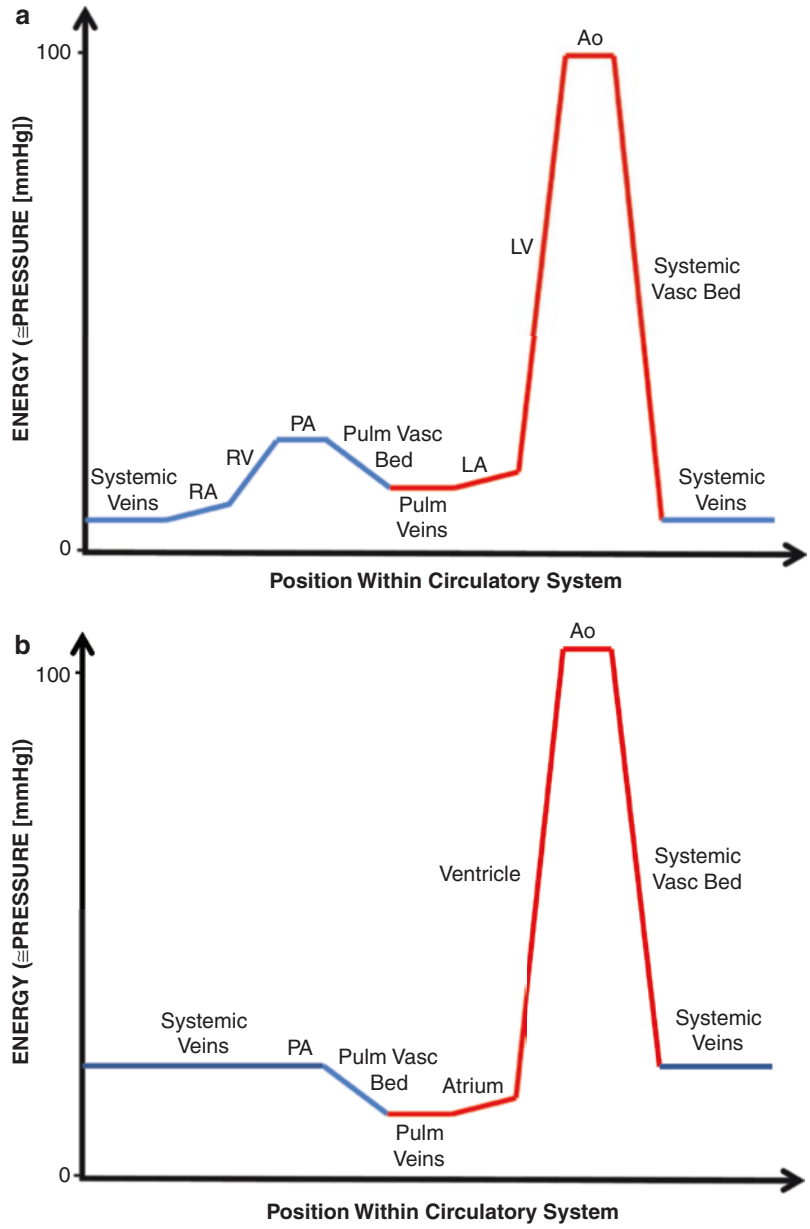


Fig. 15.2 Energetics of the normal, biventricular circulation (**a**) compared to the Fontan circulation (**b**). In the normal circulation the systemic venous pressure is low and the right ventricle provides most of the energy required to perfuse the lungs. In the Fontan circulation, the lungs are perfused by the systemic venous system and the pressure in the systemic veins is abnormally high. This pressure is ultimately derived from work performed by the (single) systemic ventricle. The pulmonary venous pressure and ventricular end diastolic pressure may be low, as the filling of the ventricle is limited by the passive blood flow returning to it from the lungs. At an equivalent cardiac output, the amount of pressure-volume work performed by the ventricle is slightly higher than the normal left ventricle (in a biventricular circulation) because the Fontan patient's ventricle must provide the energy to pump the blood through the systemic *and* pulmonary circulations. For this theoretical illustration, which resembles subjects at rest, cardiac output in the two circulations was assumed to be equivalent in order to contrast the differences in energetics (i.e., pressure-volume work). In reality, compared to individuals with normal biventricular circulations, the Fontan patient also tends to adapt to the challenges posed by his/her unnatural circulation by relying more on oxygen extraction and less on cardiac output for any given metabolic rate or $\dot{V}_{O2}$. Abbreviations: Ao aorta, LA left atrium, LV left ventricle, PA pulmonary artery, pulm pulmonary, vasc vascular. Pressures in arteries and veins are mean pressures

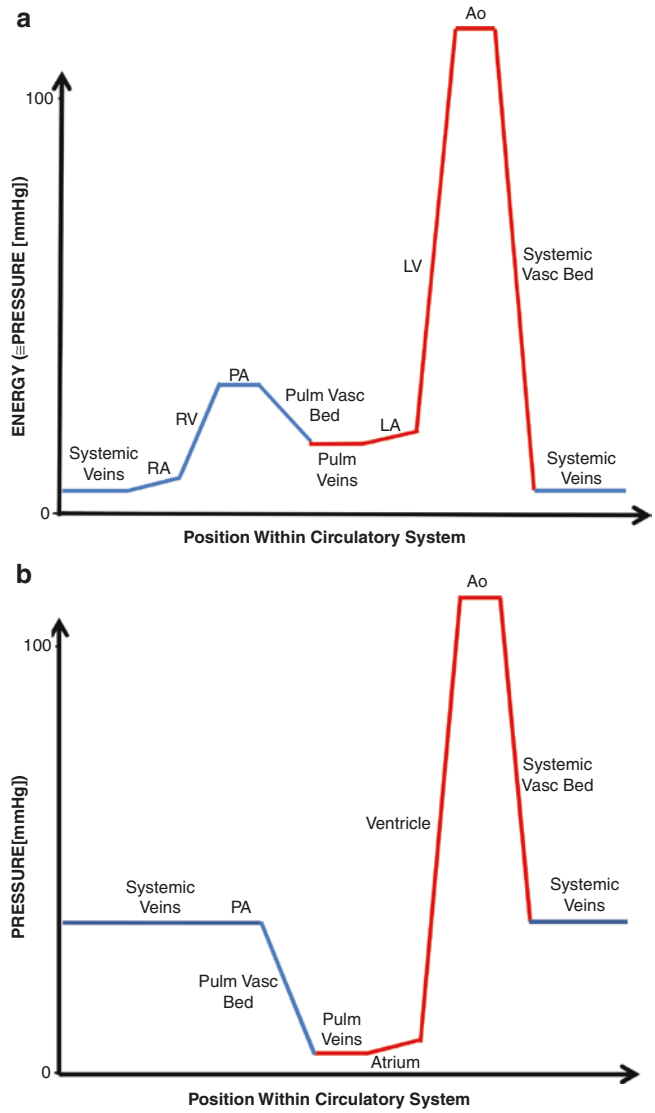


Fig. 15.3 Contrast between the hemodynamics of a normal biventricular circulation (**a**) and Fontan circulation (**b**) at peak exercise. In the biventricular circulation, there is a five-fold increase in cardiac output over resting values. In the typical Fontan patient the increase is much more modest. In the biventricular circulation, the right ventricle (RV) pumps blood into the pulmonary artery (PA), raising PA pressures significantly over resting values and far above right atrial pressure. Left atrial pressure also rises as the left ventricle moves up its Starling curve. Pulmonary vascular resistance declines, so that the transpulmonary gradient increases only modestly. In most subjects with biventricular circulations, the increase in cardiac output during exercise is limited primarily by the factors related to ventricular performance. In the Fontan circulation, systemic venous pressure rises, but the rise is limited by the systemic venous capacitance. In the absence of an RV, there is no augmentation of pressure between the systemic veins and the PAs. In addition, the pulmonary vascular resistance often does not decline as robustly as it does in a normal individual. Consequently, there is a larger pressure drop across the pulmonary vascular bed (despite the fact that cardiac output and pulmonary blood flow are lower than in the normal subject) and the systemic ventricular filling pressures are even lower than at rest; i.e., the ventricle is even more preload deprived. It is the factors limiting blood flow through the lungs (i.e., pulmonary vascular resistance and the physiological constraints on the increase in systemic venous and pulmonary artery pressures), rather than ventricular performance, that limit the augmentation of cardiac output during exercise. Note, because the cardiac output is significantly higher in the biventricular circulation (in contrast to the assumptions in Fig. 15.2), the pressure-volume work performed by the normal LV in a biventricular circulation is much greater than the preload-deprived ventricle of the Fontan circulation. Consequently, the biventricular circulation can support a much higher level of physical activity [38]. Abbreviations: Ao aorta, LA left atrium, LV left ventricle, PA pulmonary artery, pulm pulmonary, vasc vascular

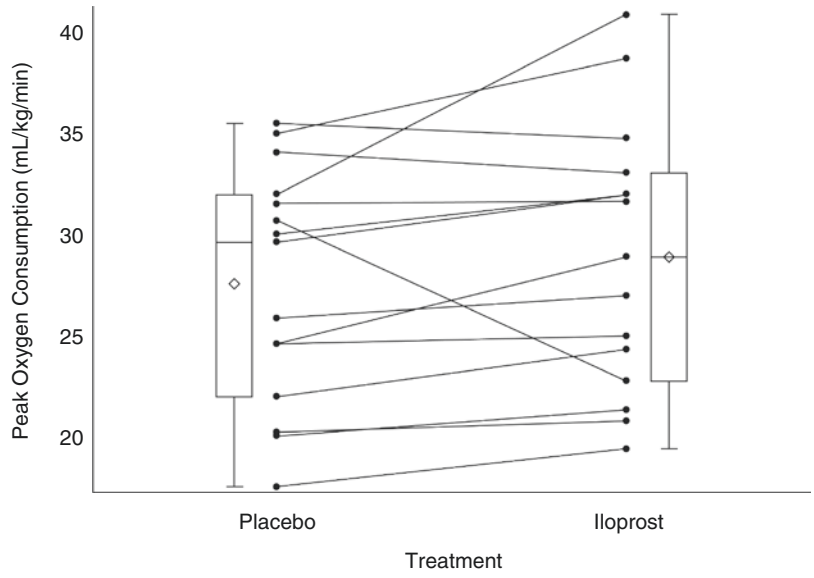


Fig. 15.4 Effect of iloprost on peak $\dot{V}_{O_2}$. The peak $\dot{V}_{O_2}$ on the exercise test preceded by iloprost administration was higher than on the test preceded by placebo for all 9 patients whose peak $\dot{V}_{O_2}$ was <30 ml/kg/min on the exercise test preceded by placebo administration. (Reprinted with permission from [45])

concerns regarding the health of the Fontan patient's pulmonary vascular bed and its ability to perform this important physiologic function. Abnormalities of endothelial function, microscopic structure, large pulmonary vessels, nitric oxide synthase expression and pulmonary vascular resistance have been described [8, 9, 39–44].

These studies have motivated investigators to evaluate the effect of pulmonary vasodilators on the exercise function of patients with Fontan physiology. One study investigated the acute effect of iloprost (a rapid-onset, pulmonary selective, inhaled prostacyclin analog with potent pulmonary vasodilator properties) on the exercise function of Fontan patients [45]. An in-depth analysis of this study is worthwhile, as it illustrates how data from CPET studies, and an understanding of exercise physiology, can be leveraged to maximize the knowledge that can be derived from clinical research.

This was a small (15 subject), double-blind, placebo, controlled crossover trial. Each subject performed 2 CPETs, one immediately after receiving a nebulized dose of either iloprost or placebo, and a second ~4 weeks later, after receiving the other agent. The order in which the agents were administered was randomized and all parties were blinded. In 12/15 subjects, the peak $\dot{V}_{O_2}$ (p <0.04) and the oxygen pulse at peak exercise (p <0.001) were better after iloprost administration compared to placebo administration. Moreover, in all 9 subjects with control peak $\dot{V}_{O_2}$ <30 ml/kg/min, peak $\dot{V}_{O_2}$ was better following iloprost (Fig. 15.4) [45]. These data suggest that in Fontan patients with relatively well-preserved exercise function, pulmonary vasodilator therapy may be of little benefit, probably because these patients have relatively healthy pulmonary vascular beds. However, in patients with poor exercise function, pulmonary vasodilator therapy is beneficial, presumably because their pulmonary vascular beds are dysfunctional; i.e., their pulmonary vascular resistance does not decline normally with exercise. This vascular dysfunction, which is partially reversed by the iloprost treatment, is often an important factor contributing to the Fontan patient's poor exercise function.

Iloprost had little or no effect upon the oxygen saturation or heart rate at peak exercise. In addition, because inhaled iloprost has little or no systemic effects, it is unlikely that it affected oxygen extraction or mixed venous oxygen content at peak exercise. Hence the observed increase in oxygen pulse was almost certainly due to an increase in the forward stroke volume following iloprost inhalation.

A better understanding of the physiologic effects of iloprost in Fontan patients may be

gained by a manipulation of the Fick equation where the oxygen pulse is viewed not as the amount of oxygen consumed per heartbeat but as the (mathematically equivalent but conceptually different) amount of oxygen added to the blood by the lungs per heartbeat:

$$\begin{aligned} O_2P &= \left[\text{amount of } O_2 \textit{ added to blood per heart beat}\right] \\ &= \dot{V}_{O2} / HR = SV \times \left[C_{pv}O_2 - C_{pa}O_2\right] \\ &= \left[PBF / HR\right] \times \left[C_{pv}O_2 - C_{pa}O_2\right] \\ &\quad - \\ &\quad \frac{\left(P_{PA} - P_{LA}\right)}{PVR} \end{aligned}$$

O_2P oxygen pulse, SV forward stroke volume, $C_{pv}O_2$ pulmonary venous oxygen content, $C_{pa}O_2$ pulmonary arterial oxygen content, PBF pulmonary blood flow, HR heart rate, P_{PA} mean pulmonary artery pressure, P_{LA} mean left atrial pressure, PVR pulmonary vascular resistance

As noted previously, the heart rate at peak exercise was similar on the iloprost and placebo studies. Moreover, it is unlikely that iloprost had an effect upon the pulmonary venous content (because iloprost would not be expected to cause pulmonary parenchymal disease and pulmonary venous desaturation) or peak exercise pulmonary arterial oxygen content (because iloprost should not be expected to affect the extraction of oxygen at peak exercise). Consequently, on the basis of this line of reasoning, it appears that the increase in oxygen pulse associated with iloprost administration was due largely to an increase in pulmonary blood flow. Iloprost is also unlikely to have increased the pressure in the Fontan circulation (i.e., pulmonary arterial pressure, because the pressure rise within the Fontan circuit is limited by the prodigious capacitance of the systemic venous circulation) or to have significantly affected the left atrial pressure (and hence the transpulmonary pressure gradient) at peak exercise. Thus, because pulmonary blood flow is equal to the transpulmonary pressure gradient divided by PVR, this equation implies that the increase in oxygen pulse was related primarily to iloprost's enhancement of the exercise-induced decline in PVR. The increased pulmonary blood flow that resulted from the iloprost-induced pulmonary vasodilation in turn led to improved ventricular preload, higher ventricular stroke volume, and better exercise function.

The effect of oral pulmonary vasodilators on the exercise function of Fontan patients has also been studied. While more practical for clinical use, oral agents may affect both the systemic and pulmonary vascular beds—a property that complicates efforts to understand their hemodynamic and clinical effects. Giardini et al. found that medically stable Fontan patients who received a single dose of sildenafil, a phosphodiesterase 5 inhibitor, achieved an increase in peak V_{O2} of 9.4 ± 5.2% while a control group of similar Fontan patients had no change; 0.3 ± 4.1% [46]. Based upon data from measurements of pulmonary blood flow using inert gas rebreathing technology, they concluded that the improvement was related to an increase in pulmonary blood flow. This study was not blinded, however, and it is hard to know whether the observed improvement was due to physiologic effects of the drug or to increased encouragement and/or increased effort on the part of the patients as they were all aware that the medication had been administered. Van De Bruaene et al. reported that a single relatively high dose of sildenafil improved cardiac output during exercise in association with a decrease in total pulmonary resistance and increase in stroke volume as estimated by supine cardiac magnetic resonance. Notably, ventricular end diastolic volume tended to be lower following sildenafil administration – an unexpected finding if increased pulmonary

vasodilation and increased pulmonary blood flow were the sole factors accounting for the improved stroke volume and peak $\dot{V}_{O2}$ [14]. In contrast to these studies, in a double-blind, placebo-controlled crossover trial, Goldberg et al. did not detect an improvement in peak $\dot{V}_{O2}$ following a 6-week course of sildenafil therapy; although there were hints of subtle improvements in submaximal exercise parameters [47].

Hebert et al. reported that, in a randomized, placebo-controlled, blinded study, 14 weeks of treatment with the endothelin receptor antagonist bosentan was associated with a modest (7.0%) increase in peak $\dot{V}_{O2}$, compared to an only 2.1% increase in the placebo group [10]. A study by Cedars et al. reported similar results in a randomized-controlled, blinded study [48]. In contrast, a multicenter open-label trial by Schuuring et al. did not detect a beneficial effect of bosentan [49].

Chronotropic Insufficiency

A chronotropic defect may also cause and/or contribute to exercise dysfunction in Fontan patients. Many patients with Fontan palliation have a variable degree of chronotropic insufficiency that, especially when severe, will adversely affect exercise function [10, 25, 27]. Moreover, the Fontan patient's ability to compensate for a decreased chronotropic response to exercise by increasing his/her stroke volume response to exercise is limited. Consequently, in these cases, appropriate pacemaker therapy can significantly improve exercise function. That said, while this intervention is often clearly indicated (e.g., with complete heart block), it can be challenging to determine whether chronotropic insufficiency is contributing to patient symptoms in the context of sinus node dysfunction, especially when it is not severe.

Other Causes of Exercise Dysfunction

Studies have also found that Fontan patients often have skeletal muscle abnormalities [36, 50], which may adversely affect the Fontan patient's ability to augment preload, reduce afterload, and increase oxygen extraction during exercise. The potential contribution of skeletal muscles' pumping action to the Fontan patient's exercise hemodynamics can be readily appreciated from the illustration of circulatory system energetics found in Fig. 15.1. It is therefore not surprising that numerous studies have found that exercise training has a beneficial effect upon the exercise function of patients with Fontan circulations [51–55].

Venous return during exercise may also be influenced by systemic venous compliance and function. Studies have found that systemic venous compliance is markedly reduced in the stable young Fontan circulation, presumably as a compensatory mechanism to prevent orthostatic hypotension in the absence of a subpulmonary pump [56, 57]. In one case report clinical deterioration and exercise limitation was attributed to a hemodynamically inappropriate increase in venous compliance that resulted in impaired venous return and pulmonary blood flow [22]. This observation takes on additional importance when one recognizes that oral pulmonary vasodilators, such as phosphodiesterase 5 inhibitors, also have systemic venodilating effects. It should be further noted that while venous dilation may reduce the potential positive, pulmonary vasodilator-related impact of these agents on exercise capacity, venodilation may also reduce systemic venous pressure. Consequently, although these agents may not effectively increase peak $\dot{V}_{O2}$, they might permit Fontan patients to perform physical activities at a lower systemic venous pressure and may thereby reduce some of the long-term deleterious effects of systemic venous hypertension.

Fenestration Closure

Right-to-left shunting between the high pressure Fontan pathway and the (obligatively lower pressure) pulmonary venous atrium is present in all Fontan patients with patent fenestrations and results in arterial desaturation. Closing these communications will reduce right-to-left shunting and improve arterial saturation. Some have

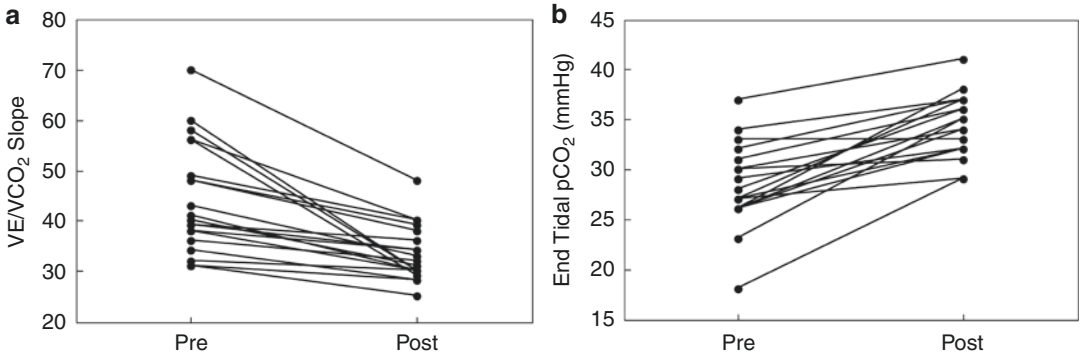


Fig. 15.5 Changes in ventilatory function during exercise after fenestration closure. Fenestration closure-associated changes in each individual patient's minute ventilation/carbon dioxide elimination ($\dot{V}_E/\dot{V}_{CO2}$) slope (**a**), end-tidal partial pressure of carbon dioxide (pCO_2) at the ventilatory anaerobic threshold (**b**). The $\dot{V}_E/\dot{V}_{CO2}$ slope fell in every patient. The end-tidal pCO_2 rose and the end-tidal pO_2 fell in 19 of 20 patients. Post post-fenestration closure, Pre pre-fenestration closure. (Reprinted with permission from [58])

hoped that this intervention would also have a salutary effect upon exercise capacity (peak $\dot{V}_{O2}$). This hypothesis was tested by Meadows et al. in a study of 20 Fontan patients who underwent CPET before and after transcatheter fenestration closure [58]. Fenestration closure was associated with a small but statistically insignificant improvement in peak $\dot{V}_{O2}$. Fenestration closure was also associated with a dramatic and consistent decrease in the $\dot{V}_E/\dot{V}_{CO2}$ slope (all 20 patients; Fig. 15.5 [58]) and a dramatic, consistent increase in the end-tidal pCO_2 (in 19/20 patients). These changes are predictable based upon the physiology of right-to-left shunts described in Chap. 12. During exercise, the right-to-left shunting blood's oxygen content is low and the CO_2 content is high. When the CO_2-rich blood enters the systemic arterial circulation, the increased pCO_2 is sensed by arterial chemoreceptors triggering homeostatic mechanisms that cause increased ventilation (which raises the $\dot{V}_E/\dot{V}_{CO2}$ slope) in order to reduce the pCO_2 of the blood returning from the lungs (which is reflected by the end-tidal pCO_2) so that the pCO_2 of the systemic arterial blood (which is the mixture of the pulmonary venous and right-to-left shunting blood) is restored to normal levels. It should be noted that, although improved, the Fontan patients' $\dot{V}_E/\dot{V}_{CO2}$ slopes remained abnormally high and their end-tidal pCO_2 levels remained abnormally low, even after fenestration closure, largely because the pulmonary blood flow maldistribution and consequent V/Q mismatch associated with the absence of a sub-pulmonary ventricle.

The absence of a significant improvement in peak $\dot{V}_{O2}$ can also be understood from an analysis of the physiology of Fontan fenestration closure. Once again, this physiology is best appreciated from the modification of the Fick equation whereby the oxygen pulse is viewed not as the product of forward stroke volume and oxygen extraction but as the (mathematically equivalent but conceptually different) product of the amount of blood flowing to the lungs per heartbeat times the amount of oxygen added by the lungs to each liter of blood:

$$
\begin{aligned}
O_2P &= \left[\text{amount of } O_2 \textit{ added to blood per heart beat}\right] \\
&= \dot{V}_{O2}/HR = SV \times \left[C_{pv}O_2 - C_{pa}O_2\right] \\
&= \left[PBF/HR\right] \times \left[C_{pv}O_2 - C_{pa}O_2\right] \\
&\quad \frac{\left(\bar{P}_{PA} - P_{LA}\right)}{PVR}
\end{aligned}
$$

Fenestration closure would not be expected to change $C_{pv}O_2$, $C_{pa}O_2$ or heart rate at peak exercise. Nor would it have an effect upon the pulmonary vascular resistance. At peak exercise the Fontan pressure rises to as high as the systemic venous capacitance will allow, and this value would not be affected by fenestration closure. Finally, closing a fenestration is unlikely to have much of an effect upon a Fontan patient's left atrial pressure at peak exercise. Thus, none of the variables that determine the oxygen pulse (or $\dot{V}_{O2}$) at peak exercise are significantly affected by fenestration closure, and it is therefore not surprising that significant changes in these parameters were not observed.

It is instructive to compare the physiologic changes associated with fenestration closure to those associated with transcatheter closure of a pulmonary arteriovenous malformation (AVM) in a patient with an otherwise normal, biventricular circulation [59–61]. As with a Fontan fenestration, the pulmonary AVM results in a right-to-left shunt with deoxygenated, hypercapneic systemic venous blood bypassing the alveoli and mixing with the pulmonary venous blood returning from the alveoli. Consequently, these patients have elevated $\dot{V}_E/\dot{V}_{CO2}$ slopes and low end tidal pCO_2 levels [59] for physiologic reasons identical to those encountered in Fontan patients with patent fenestrations. When these lesions are successfully closed, however, the $\dot{V}_E/\dot{V}_{CO2}$ slopes and end tidal pCO_2 levels normalize because, unlike Fontan patients, they do not have persistent V/Q mismatch secondary to the pulmonary blood flow maldistribution associated with the absence of a subpulmonary ventricle. Moreover, in contrast to the Fontan patients undergoing fenestration closure, in a patient with isolated pulmonary AVM the peak $\dot{V}_{O2}$ rises dramatically following closure of the malformation. The reason for this discrepant response is readily appreciated from the equation above, if one understands the "PBF" in that equation to be the "effective" pulmonary blood flow (i.e., the blood flow that goes to the alveoli), the "PVR" to be the pulmonary *arteriolar* resistance, and the "C_{pv}" to be the oxygen content of blood returning from the alveoli. Prior to closure of the malformation, the low-resistance AVM steals blood from the pulmonary artery and lowers the mean pulmonary artery pressure, resulting in decreased effective pulmonary blood flow. Following closure, the mean pulmonary artery pressure will be higher, as there no longer will be run-off of blood through the low-resistance AVM. The equation demonstrates that, if all the other variables remain unchanged (as is likely), the pulmonary blood flow, stroke volume, oxygen pulse, and peak $\dot{V}_{O2}$ will all be higher following successful AVM occlusion.

The Fontan Circulation as a Benchmark for Other Congenital Heart Defects

It is often worthwhile to utilize exercise data from Fontan patients as a benchmark against which to compare patients with other congenital heart defects. This undertaking is particularly relevant when applied to diagnoses that may be amenable to single ventricle or biventricular palliation. Although it may seem reasonable to assume that biventricular palliation is usually preferable, the reality is more complex. For instance, among patients with pulmonary atresia with intact ventricular septum, studies have found that the peak $\dot{V}_{O2}$ of those who have undergone biventricular repair is not significantly better than that of those who have undergone Fontan palliation [62, 63]. The biventricular repair patients appear to segregate into two groups: those whose peak $\dot{V}_{O2}$ is significantly better than those of the Fontan patients, and those whose peak $\dot{V}_{O2}$ is similar to or worse than the Fontan patients. The tricuspid valve Z score on a neonatal echocardiogram was found to be the factor most strongly associated with poor exercise function in the biventricular group [63]. It seems that patients with more severe degrees of initial right heart hypoplasia who are forced down a biventricular pathway incur a greater risk of late deficits in aerobic capacity. Moreover, the Fontan patients with the

worst aerobic capacity were those in whom Fontan palliation was undertaken later, suggesting that delaying Fontan completion by attempting to maintain a failing biventricular repair may ultimately cause long-term limitation of exercise function [62]. These data therefore question the wisdom of trying to create a biventricular circulation in patients with severe right ventricular hypoplasia. It must be recognized, however, that although exercise capacity is an important measure in itself and is an excellent surrogate for clinical outcomes in almost all situations that have been studied, it should not be assumed to predict long-term outcomes without empiric validation. The long-term outcomes of biventricular repair of marginal circulations remain to be defined and must await long-term follow-up studies of sizable cohorts undergoing single ventricle vs. biventricular repairs of borderline circulations.

It should also be noted that the $\dot{V}_E/\dot{V}_{CO2}$ slope of patients with Fontan palliation was significantly higher than that of patients with biventricular palliation [62], once again highlighting the importance of the subpulmonary ventricle in maintaining pulmonary artery pulsatility, normal pulmonary blood flow distribution, normal V/Q matching, and efficient gas exchange during exercise. The importance of these physiologic functions should also be taken into consideration when making clinical decisions regarding the management of patients with hypoplastic right ventricles.

Analogous studies in patients with left ventricular hypoplasia have not yet been undertaken, undoubtedly because fetal interventions for severe aortic stenosis and the concept of attempting to "recruit" a small left ventricle with the hope that it will ultimately serve as the systemic ventricle have only been recently introduced. Consequently, there are very few survivors of this management strategy who are old enough to perform a cardiopulmonary exercise test. However, there are other exercise studies, in slightly different patient populations, that may be informative. It has been found that the exercise function of children and adolescents with biventricular circulations following interventions for severe aortic stenosis within the first 6 months of life (including some who had Congenital Heart Surgeon Society scores and modified Rhodes stratification scores [64] that predicted them to have a survival advantage with single-ventricle palliation) tends to be better than that of Fontan patients [65]. If this were not the case, the rationale for pursuing an aggressive approach toward fetal aortic stenosis and/or the recruitment of a congenitally hypoplastic left ventricle would be weakened. However, the superior exercise function of this group of patients constitutes an argument in favor of ongoing attempts to pursue and improve this therapeutic approach.

Prognostic Value of Cardiopulmonary Exercise Testing Data in Patients with Fontan Circulations

A number of studies have established the prognostic value of exercise testing data in patients with Fontan circulations. In a study of 146 adolescent and young adult Fontan patients, Fernandes et al. found that the hazard for death for patients with a peak oxygen consumption of <16.6 mL/kg/min was 7.5 times that of patients with a higher peak $\dot{V}_{O2}$. Similarly, the hazard ratio for patients with peak exercise heart rates of <123 bpm was 10.6 (95% CI 3.0, 37.1; P <0.0002; Fig. 15.6) [30]. Moreover, the combination of peak heart rate ≥123, peak $\dot{V}_{O2}$ ≥16.6 ml/kg/min and VAT ≥9.0 ml/kg/min conferred a 98% negative predictive value for mortality over a median of 3.7 years of follow-up [30]. Similarly, Inuzaka et al. found that the heart rate reserve and %predicted peak $\dot{V}_{O2}$ provided strong prognostic information for patients with Fontan circulations [26]. On the other hand, Diller et al. reported that CPET parameters were strongly predictive of hospitalization, but not of death [66].

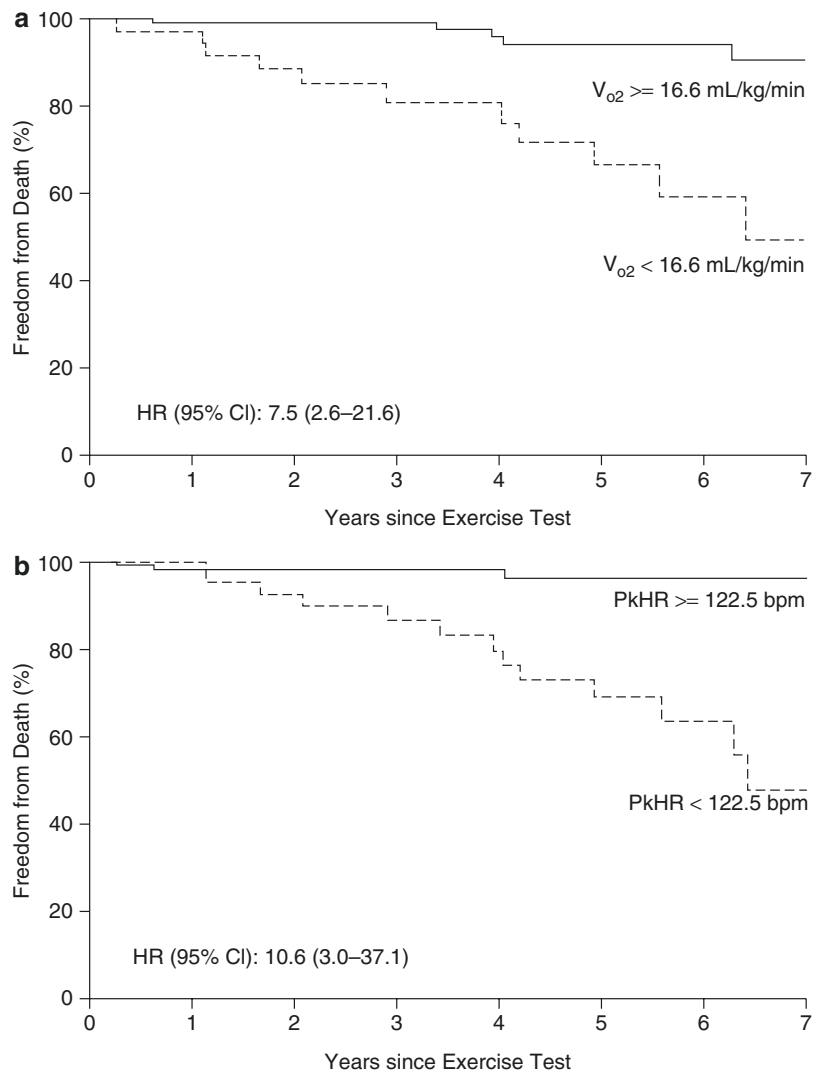


Fig. 15.6 Time to death for patients above and below the cutoff value for: (**a**) weight-*normalized* peak $\dot{V}_{O2}$ and (**b**) peak heart rate. CI confidence intervals, HR hazard ratio, PkHR heart rate at peak exercise, $\dot{V}_{O2}$ oxygen consumption. (Reprinted with permission from [30])

There has also been research on serial changes in peak $\dot{V}_{O2}$ over time. Egbe et al. reported that a decline in %predicted peak $\dot{V}_{O2}$ of >3 percentage points per year was a powerful predictor of subsequent adverse cardiovascular events [67]. Cunningham and colleagues reported that each 10% decline in peak $\dot{V}_{O2}$ between 2 CPETs performed 6–30 months apart was associated with a two-fold increased risk of a combined endpoint of death or cardiac transplantation, even after adjusting for the baseline value of peak $\dot{V}_{O2}$. These reports suggest that serial changes in aerobic capacity provide substantial information beyond single measurements [68].

Prototypical Patient

The patient was a 17-year-old adolescent who was born with dextrocardia, tricuspid atresia, and transposition of the great arteries. A pulmonary artery band was placed when he was 2 months old and he underwent a Damus-Kaye-Stansel procedure and lateral tunnel fenestrated Fontan

Table 15.2 Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	31.7
Peak $\dot{V}_{O2}$ (%predicted)	66
Peak work rate (W)	192
Peak work rate (%predicted)	68
Peak RER	1.11
Peak O_2 pulse (%predicted)	76
Peak heart rate (bpm)	164
Peak heart rate (%predicted)	95
Heart rate increase	Excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	32
End-tidal pCO_2 at VAT (mm Hg)	28
End-tidal pCO_2 during exercise	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	35
Forced vital capacity (%predicted)	81
FEV1 (%predicted)	81
FEF 25–75 (%predicted)	70
Breathing reserve	38
Rhythm	Atrial throughout study
Blood pressure response	Normal
Oxygen saturation at rest (%)	93
Oxygen saturation at peak exercise (%)	92

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

procedure when he was 2.5 years old. The fenestration was closed electively when he was 7 years old. At the time of the exercise test (Table 15.2 and Fig. 15.7), he was asymptomatic. He worked out at a gym and/or at home several times a week and felt that his exercise capacity was normal. His echocardiogram revealed good ventricular function, mild mitral regurgitation, and an unobstructed Fontan pathway. No evidence of a residual fenestration was detected. The exercise test was obtained to further characterize his current cardiologic status.

Based upon his peak RER the patient expended a good effort. His peak work rate and peak $\dot{V}_{O2}$ were moderately depressed. The $\dot{V}_{O2}$ at the VAT was also low. The low peak exercise values appeared to be related to a low oxygen pulse. Although he had an ectopic atrial rhythm, his ability to increase his heart rate during exercise was well preserved. He had excessive ventilation associated with a low end-tidal pCO_2 during exercise. Mild arterial oxygen desaturation was present at rest and at peak exercise. Baseline spirometry revealed a mild, primarily obstructive pattern. His breathing reserve was normal.

The exercise test data revealed that, although he was asymptomatic and believed he had normal exercise capacity, objective measurements revealed that his exercise function was in fact moderately depressed. The difference between his perception and reality probably related, at least in part, to the fact that he was born with serious congenital heart disease and had never known what it is like to have a normal heart. The decreased exercise tolerance appeared to be due to a low stroke volume response to exercise, despite the presence of normal left ventricular function on echocardiography and only mild mitral regurgitation. This phenomenon probably reflects the fact that his ability to increase his stroke volume during exercise was limited by his ability to increase blood flow through his passively perfused lungs during exercise. The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO2 during exercise are typical of Fontan patients and result from ventilation/perfusion mismatch secondary to the pulmonary blood flow maldistribution in the passively perfused, non-pulsatile pulmonary circulation. The spirometric abnormalities are also typical of patients with complex congenital heart disease who have undergone multiple surgical procedures.

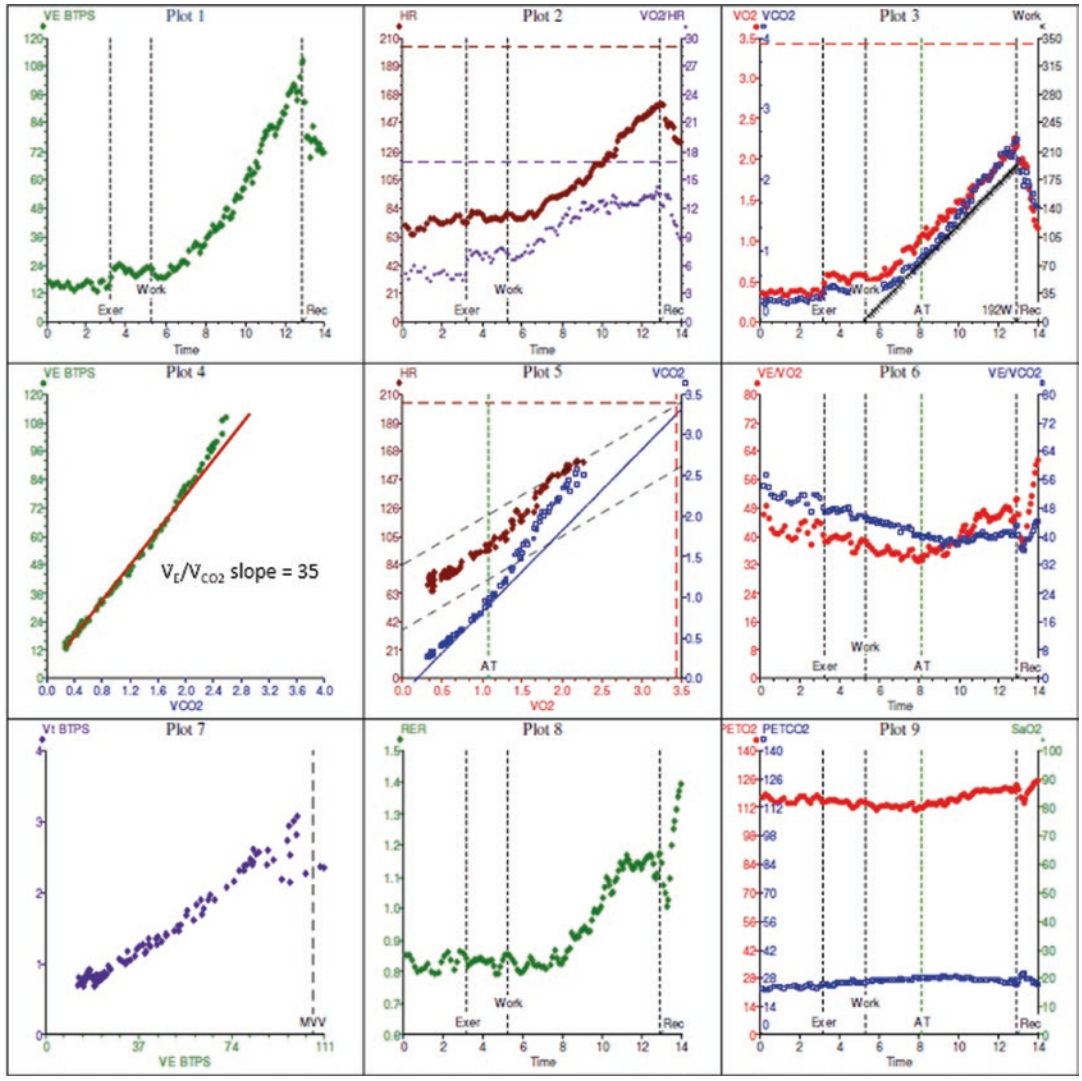


Fig. 15.7 Nine-panel graph from prototypical Fontan patient. CI confidence intervals, HR hazard ratio, PkHR heart rate at peak exercise, V_{O2} oxygen consumption

References

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax. 1971;26:240–8.
2. Fontan F, Mounicot FB, Baudet E, Simonneau J, Gordo J, Gouffrant JM. ["Correction" of tricuspid atresia. 2 cases "corrected" using a new surgical technic]. Ann Chir Thorac Cardiovasc. 1971;10(1):39–47.
3. Pundi KN, Johnson JN, Dearani JA, Pundi KN, Li Z, Hinck CA, et al. 40-year follow-up after the Fontan operation: long-term outcomes of 1052 patients. J Am Coll Cardiol. 2015;66(15):1700–10.
4. Veldtman GR, Opotowsky AR, Wittekind SG, Rychik J, Penny DJ, Fogel M, et al. Cardiovascular adaptation to the Fontan circulation. Congenit Heart Dis. 2017;12(6):699–710.
5. Jolley M, Colan SD, Rhodes J, DiNardo J. Fontan physiology revisited. Anesth Analg. 2015;121(1):172–82.
6. Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. Heart. 2016;102(14):1081–6.
7. Ben Shachar G, Fuhrman BP, Wang Y, Lucas RV Jr, Lock JE. Rest and exercise hemodynamics after the Fontan procedure. Circulation. 1982;65(6):1043–8.
8. Barber G, Di Sessa T, Child JS, Perloff JK, Laks H, George BL, et al. Hemodynamic responses to isolated increments in heart rate by atrial pacing after a Fontan procedure. Am Heart J. 1988;115(4):837–41.

9. Goldstein BH, Connor CE, Gooding L, Rocchini AP. Relation of systemic venous return, pulmonary vascular resistance, and diastolic dysfunction to exercise capacity in patients with single ventricle receiving Fontan palliation. Am J Cardiol. 2010;105(8):1169–75.
10. Hebert A, Jensen AS, Mikkelsen UR, Idorn L, Sorensen KE, Thilen U, et al. Hemodynamic causes of exercise intolerance in Fontan patients. Int J Cardiol. 2014;175(3):478–83.
11. Legendre A, Guillot A, Ladouceur M, Bonnet D. Usefulness of stroke volume monitoring during upright ramp incremental cycle exercise in young patients with Fontan circulation. Int J Cardiol. 2017;227:625–30.
12. Shafer KM, Garcia JA, Babb TG, Fixler DE, Ayers CR, Levine BD. The importance of the muscle and ventilatory blood pumps during exercise in patients without a subpulmonary ventricle (Fontan operation). J Am Coll Cardiol. 2012;60(20):2115–21.
13. Navaratnam D, Fitzsimmons S, Grocott M, Rossiter HB, Emmanuel Y, Diller GP, et al. Exercise-induced systemic venous hypertension in the Fontan circulation. Am J Cardiol. 2016;117(10):1667–71.
14. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, et al. Sildenafil improves exercise hemodynamics in Fontan patients. Circ Cardiovasc Imaging. 2014;7(2):265–73.
15. Gewillig MH, Lundstrom UR, Bull C, Wyse RK, Deanfield JE. Exercise responses in patients with congenital heart disease after Fontan repair: patterns and determinants of performance. J Am Coll Cardiol. 1990;15(6):1424–32.
16. Senzaki H, Masutani S, Kobayashi J, Kobayashi T, Sasaki N, Asano H, et al. Ventricular afterload and ventricular work in Fontan circulation: comparison with normal two-ventricle circulation and single-ventricle circulation with Blalock-Taussig shunts. Circulation. 2002;105(24):2885–92.
17. Brili SV, Alexopoulos NA, Barberis VI, Gatzoulis MA, Barbetseas J, Chrysohoou C, et al. Dobutamine stress echocardiography for the evaluation of cardiac reserve late after Fontan operation. Hell J Cardiol. 2007;48(5):252–7.
18. Wong J, Pushparajah K, de Vecchi A, Ruijsink B, Greil GF, Hussain T, et al. Pressure-volume loop-derived cardiac indices during dobutamine stress: a step towards understanding limitations in cardiac output in children with hypoplastic left heart syndrome. Int J Cardiol. 2017;230:439–46.
19. Bossers SS, Kapusta L, Kuipers IM, van Iperen G, Moelker A, Kroft LJ, et al. Ventricular function and cardiac reserve in contemporary Fontan patients. Int J Cardiol. 2015;196:73–80.
20. Robbers-Visser D, Jan Ten Harkel D, Kapusta L, Strengers JL, Dalinghaus M, Meijboom FJ, et al. Usefulness of cardiac magnetic resonance imaging combined with low-dose dobutamine stress to detect an abnormal ventricular stress response in children and young adults after Fontan operation at young age. Am J Cardiol. 2008;101(11):1657–62.
21. Senzaki H, Masutani S, Ishido H, Taketazu M, Kobayashi T, Sasaki N, et al. Cardiac rest and reserve function in patients with Fontan circulation. J Am Coll Cardiol. 2006;47(12):2528–35.
22. Opotowsky AR, Halpern D, Kulik TJ, Systrom DM, Wu F. Inadequate venous return as a primary cause for Fontan circulatory limitation. J Heart Lung Transplant. 2014;33(11):1194–6.
23. Rao RP, Danduran MJ, Hoffman GM, Ghanayem NS, Berger S, Frommelt PC. Cerebral hemodynamics in the presence of decreased systemic venous compliance in patients with Fontan physiology may limit anaerobic exercise capacity. Pediatr Cardiol. 2010;31(2):208–14.
24. Troutman WB, Barstow TJ, Galindo AJ, Cooper DM. Abnormal dynamic cardiorespiratory responses to exercise in pediatric patients after Fontan procedure. J Am Coll Cardiol. 1998;31(3):668–73.
25. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li J, et al. A cross-sectional study of exercise performance during the first two decades of life following the Fontan operation. J Am Coll Cardiol. 2008;52:99–107.
26. Inuzuka R, Diller GP, Borgia F, Benson L, Tay ELW, Alonso-Gonzalez R, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation. 2012;125(2):250–9.
27. Durongpisitkul K, Driscoll DJ, Mahoney DW, Wollan PC, Mottram CD, Puga FJ, et al. Cardiorespiratory response to exercise after modified Fontan operation: determinants of performance. J Am Coll Cardiol. 1997;29(4):785–90.
28. Driscoll DJ, Feldt RH, Mottram CD, Puga FJ, Schaff HV, Danielson GK. Cardiorespiratory response to exercise after definitive repair of univentricular atrioventricular connection. Int J Cardiol. 1987;17(1):73–81.
29. Driscoll DJ, Danielson GK, Puga FJ, Schaff HV, Heise CT, Staats BA. Exercise tolerance and cardiorespiratory response to exercise after the Fontan operation for tricuspid atresia or functional single ventricle. J Am Coll Cardiol. 1986;7(5):1087–94.
30. Fernandes SM, Alexander ME, Graham DA, Khairy P, Clair M, Rodriguez E, et al. Exercise testing identifies patients at increased risk for morbidity and mortality following Fontan surgery. Congenit Heart Dis. 2011;6:294–303.
31. Giardini A, Hager A, Napoleone CP, Picchio FM. Natural history of exercise capacity after the Fontan operation: a longitudinal study. Ann Thorac Surg. 2008;85:818–22.
32. Nir A, Driscoll DJ, Mottram CD, Offord KP, Puga FJ, Schaff HV, et al. Cardiorespiratory response to exercise after the Fontan operation: a serial study. J Am Coll Cardiol. 1993;22(1):216–20.
33. Fernandes SM, McElhinney DB, Khairy P, Graham DA, Landzberg MJ, Rhodes J. Serial cardiopulmonary exercise testing in patients with previous Fontan surgery. Pediatr Cardiol. 2010;31(2):175–80.

34. Opotowsky AR, Landzberg MJ, Earing MG, Wu FM, Triedman JK, Casey A, et al. Abnormal spirometry after the Fontan procedure is common and associated with impaired aerobic capacity. Am J Physiol Heart Circ Physiol. 2014;307(1):H110–7.
35. Atz AM, Zak V, Mahony L, Uzark K, D'Agincourt N, Goldberg DJ, et al. Longitudinal outcomes of patients with single ventricle after the Fontan procedure. J Am Coll Cardiol. 2017;69(22):2735–44.
36. Greutmann M, Le TL, Tobler D, Biaggi P, Oechslin EN, Silversides CK, et al. Generalised muscle weakness in young adults with congenital heart disease. Heart. 2011;97(14):1164–8.
37. Gewillig M, Goldberg DJ. Failure of the Fontan circulation. Heart Fail Clin. 2014;10(1):105–16.
38. La Gerche A, Gewillig M. What limits cardiac performance during exercise in normal subjects and in healthy Fontan patients? Int J Pediatr. 2010;2010:791291.
39. Yin Z, Wang Z, Zhu H, Zhang R, Wang H, Li X. Experimental study of effect of Fontan circuit on pulmonary microcirculation. Asian Cardiovasc Thorac Ann. 2006;14(3):183–8.
40. Khambadkone S, Li J, de Leval MR, Cullen S, Deanfield JE, Redington AN. Basal pulmonary vascular resistance and nitric oxide responsiveness late after Fontan-type operation. Circulation. 2003;107(25):3204–8.
41. Levy M, Danel C, Laval AM, Leca F, Vouhe PR, Israel-Biet D. Nitric oxide synthase expression by pulmonary arteries: a predictive marker of Fontan procedure outcome? J Thorac Cardiovasc Surg. 2003;125(5):1083–90.
42. Mitchell MB, Campbell DN, Ivy D, Boucek MM, Sondheimer HM, Pietra B, et al. Evidence of pulmonary vascular disease after heart transplantation for Fontan circulation failure. J Thorac Cardiovasc Surg. 2004;128(5):693–702.
43. Hays BS, Baker M, Laib A, Tan W, Udholm S, Goldstein BH, et al. Histopathological abnormalities in the central arteries and veins of Fontan subjects. Heart. 2018;104(4):324–31.
44. Egbe AC, Connolly HM, Miranda WR, Ammash NM, Hagler DJ, Veldtman GR, et al. Hemodynamics of Fontan failure: the role of pulmonary vascular disease. Circ Heart Fail. 2017;10(12):1–8.
45. Rhodes J, Ubeda-Tikkanen A, Clair M, Fernandes SM, Graham DA, Milliren CE, et al. Effect of inhaled iloprost on the exercise function of Fontan patients: a demonstration of concept. Int J Cardiol 2013;168(3):2435–40.
46. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. Eur Heart J. 2008;29:1681–7.
47. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, et al. Impact of oral sildenafil on exercise performance in children and young adults after the Fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. Circulation. 2011;123(11):1185–93.
48. Cedars AM, Saef J, Peterson LR, Coggan AR, Novak EL, Kemp D, et al. Effect of ambrisentan on exercise capacity in adult patients after the Fontan procedure. Am J Cardiol. 2016;117(9):1524–32.
49. Schuuring MJ, Vis JC, van Dijk AP, van Melle JP, Vliegen HW, Pieper PG, et al. Impact of bosentan on exercise capacity in adults after the Fontan procedure: a randomized controlled trial. Eur J Heart Fail. 2013;15(6):690–8.
50. Avitabile CM, Leonard MB, Zemel BS, Brodsky JL, Lee D, Dodds K, et al. Lean mass deficits, vitamin d status and exercise capacity in children and young adults after Fontan palliation. Heart. 2014;100(21):1702–7.
51. Minamisawa S, Nakazawa M, Momma K, Imai Y, Satomi G. Effect of aerobic training on exercise performance in patients after the Fontan operation. Am J Cardiol. 2001;88(6):695–8.
52. Opocher F, Varnier M, Sanders SP, Tosoni A, Zaccaria M, Stellin G, et al. Effects of aerobic exercise training in children after the Fontan operation. Am J Cardiol. 2005;95:150–2.
53. Rhodes J, Curran TJ, Camil L, Rabideau NC, Fulton DR, Gauthier NS, et al. Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. Pediatrics. 2005;116:1339–45.
54. Sutherland N, Jones B, d'Udekem Y. Should we recommend exercise after the Fontan procedure? Heart Lung Circ. 2015;24(8):753–68.
55. Cordina RL, O'Meagher S, Karmali A, Rae CL, Liess C, Kemp GJ, et al. Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in Fontan physiology. Int J Cardiol. 2013;168(2):780–8.
56. Kelley JR, Mack GW, Fahey JT. Diminished venous vascular capacitance in patients with univentricular hearts after the Fontan operation. Am J Cardiol. 1995;76(3):158–63.
57. Krishnan US, Taneja I, Gewitz M, Young R, Stewart J. Peripheral vascular adaptation and orthostatic tolerance in Fontan physiology. Circulation. 2009;120(18):1775–83.
58. Meadows J, Lang P, Marx 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(2):108–13.
59. Rhodes J, Pollack P, Lang P. Effect of transcatheter occlusion of a pulmonary arteriovenous fistula on the cardiopulmonary response to exercise. Pediatr Cardiol. 2010;31(1):142–3.
60. Beck FJ, Neuerburg J, Sigmund M, Schmitz E, Gunther RW, Hanrath P. [An increase in cardiopulmonary exercise tolerance after the embolization of a pulmonary arteriovenous fistula]. DtschMed Wochenschr 1993;118(33):1193–1198.
61. Bye MR, Cerny FJ, Gingell RL. Increased exercise capability after repair of a pulmonary arteriovenous fistula. Chest. 1982;82(3):373–5.
62. Sanghavi DM, Flanagan M, Powell AJ, Curran T, Picard S, Rhodes J. Determinants of exercise function

following univentricular versus biventricular repair for pulmonary atresia/intact ventricular septum. Am J Cardiol. 2006;97(11):1638–43.
63. Karamlou T, Poynter JA, Walters HL 3rd, Rhodes J, Bondarenko I, Pasquali SK, et al. Long-term functional health status and exercise test variables for patients with pulmonary atresia with intact ventricular septum: a congenital heart surgeons society study. J Thorac Cardiovasc Surg. 2013;145(4):1018–25.. discussion 1025–1017
64. Rhodes LA, Colan SD, Perry SB, Jonas RA, Sanders SP. Predictors of survival in neonates with critical aortic stenosis. Circulation. 1991;84:2325–35.
65. Kipps AK, McElhinney DB, Kane J, Rhodes J. Exercise function of children with congenital aortic stenosis following aortic valvuloplasty during early infancy. Congenit Heart Dis. 2009;4(4):258–64.
66. Diller GP, Giardini A, Dimopoulos K, Gargiulo G, Muller J, Derrick G, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. Eur Heart J. 2010;31(24):3073–83.
67. Egbe AC, Driscoll DJ, Khan AR, Said SS, Akintoye E, Berganza FM, et al. Cardiopulmonary exercise test in adults with prior Fontan operation: the prognostic value of serial testing. Int J Cardiol. 2017;235:6–10.
68. Cunningham JW, Nathan AS, Rhodes J, Shafer K, Landzberg MJ, Opotowsky AR. Decline in peak oxygen consumption over time predicts death or transplantation in adults with a Fontan circulation. Am Heart J. 2017;189:184–92.

Aortic Valve Disease

16

Jonathan Rhodes

Basic Anatomy

A congenital anomaly of the aortic valve is the most common cause for aortic valve dysfunction in children. A number of anatomic variants exist characterized by variable degrees of fusion or other deformities of the aortic valve leaflets. Variable degrees of annular hypoplasia may also be present. Aortic valve prolapse into a subaortic ventricular septal defect (VSD) is an occasional cause of aortic insufficiency in childhood. Aortic insufficiency can also develop in the setting of an obstructive subaortic membrane. Although historically rheumatic fever has been a common cause of aortic insufficiency in the pediatric years, in recent decades it has become a relatively rare condition.

Severe aortic stenosis (AS) is poorly tolerated and requires surgical and/or transcatheter intervention. These interventions alter the structure of the valve and usually substantially relieve the stenosis. Of course, however, normal anatomy is not restored and residual AS and/or aortic regurgitation (AR) is common after these interventions. Aortic valve dysfunction may gradually progress over time during the pediatric years. Episodes of bacterial endocarditis may precipitate rapid deterioration in aortic valve function [1].

Exercise Hemodynamics: Aortic Regurgitation

In the presence of an incompetent aortic valve, some of the blood ejected by the left ventricle (LV) into the aorta during systole regurgitates back into the LV during the following diastole. This imposes a chronic volume overload upon the LV, which is accommodated by increased LV end-diastolic volume, increased LV compliance, and left ventricular hypertrophy. These accommodations allow the patient to maintain a normal cardiac output despite the abnormal aortic valve function [2].

Patients with significant aortic regurgitation (AR) typically have a low aortic diastolic pressure, because the runoff of blood from the aorta across the regurgitant valve during diastole causes the aortic pressure to decline more steeply. The runoff of blood into the LV will also tend to raise the LV diastolic pressure. Consequently, the coronary perfusion pressure (i.e., coronary artery pressure minus LV diastolic pressure) tends to be low; in severe cases coronary perfusion may be compromised [2].

Patients with (isolated) AR also tend to have slightly elevated aortic systolic pressure and an

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_16

increased pulse pressure (ΔP), i.e., the systolic pressure minus the diastolic pressure. This phenomenon can be understood from a rearrangement of the compliance equation:

$$\Delta P = \Delta V / \text{Compliance}$$

For the purposes of this discussion, this equation may be rewritten as:

$$(\Delta P) = (\text{Stroke Volume}) / (\text{Compliance of the Arterial Tree})$$

The stroke volume (i.e., the amount of blood pumped by the LV into the aorta) of patients with AR will always be elevated, as it is comprised of the volume of blood required to meet the metabolic demands of the body *plus* the regurgitant volume. Hence, unless the compliance of the arterial tree is markedly increased (in a magnitude comparable to the increase in stroke volume), the systolic pressure will be higher than normal and the ΔP will be increased.

Another perspective on these hemodynamics is provided by the equation:

$$\left[(\text{Mean Aortic Pressure}) - (\text{Mean Right Atrial Pressure})\right] = (\text{C.O.}) \text{ x } (\text{SVR}).$$

This equation states that the pressure drop across the systemic vascular bed equals the cardiac output times the systemic vascular resistance. If the cardiac output and systemic vascular resistance are normal, a lower-than-normal aortic diastolic pressure must be accompanied by a higher-than-normal aortic systolic pressure in order to maintain an adequate mean aortic pressure.

This discussion underscores the fact that the LV of patients with AR must perform more work (i.e., pressure times volume) than the normal left ventricle. Myocardial oxygen demand will therefore be elevated, in the setting of potentially compromised myocardial perfusion pressures and myocardial oxygen delivery. Consequently, it is not surprising that, over time, progressive LV dilation and dysfunction may develop, and the adaptive mechanisms previously described will no longer be capable of maintaining adequate cardiac output with acceptable LV filling pressure. Congestive heart failure will then develop [2, 3].

In the presence of an incompetent aortic valve, the degree of AR is determined primarily by the systemic vascular resistance (SVR) and the severity of the aortic valve incompetence. The dramatic decline in SVR that occurs during exercise promotes forward blood flow, tends to reduce the severity of the AR, and mitigates the hemodynamic impact of the valvular incompetence. In a study of 12 young (median age 22 years) patients undergoing a cardiac magnetic resonance imaging (MRI) study during exercise, Stern et al. reported that the AR fraction fell from 35% to 16% during submaximal exercise. This improvement was associated with a decline in the end-diastolic volume from 118 to 102 ml/m^2 [4]. Consequently, the *excess* pressure-volume work that the LV must perform tends to decline during exercise.

Exercise Hemodynamics: Aortic Stenosis

In patients with AS, the LV must generate increased pressure during systole in order to overcome the obstruction caused by the stenotic aortic valve. A systolic gradient therefore exists between the LV and the aorta (and coronary arteries). The increased wall stress resulting from the elevated LV systolic pressure causes the LV to develop compensatory hypertrophy and thereby normalize the wall stress (wall stress is directly proportional to the ventricular pressure and internal diameter, and inversely proportional to the wall thickness). In patients with less than severe AS, this compensatory mechanism allows the left ventricle to maintain normal or near-nor-

mal cardiac outputs even during physical activity. The LV hypertrophy will adversely affect LV diastolic function, however. Over time, myocardial fibrosis may also develop and further impair LV diastolic function [2].

The *gradient* across a stenotic aortic valve will be determined primarily by the degree of stenosis and the amount of flow going across the valve. Hence, the gradient across the aortic valve invariably increases as the cardiac output increases during exercise. The LV therefore must perform an excessive amount of pressure-volume work at rest, and in contrast to patients with AR, this burden increases during exercise. The excessive workload results in increased myocardial oxygen demand. Typically the aortic diastolic pressure is relatively well preserved (compared to patients with AR), and myocardial perfusion pressure during diastole is therefore usually fairly well maintained. LV pressure exceeds myocardial perfusion pressure during systole, however. Moreover, in the presence of diastolic dysfunction, elevated ventricular diastolic pressures can impair coronary blood flow. These conditions render the subendocardial region particularly vulnerable to myocardial ischemia, as the LV's intracavitary pressure is transmitted most forcefully to this region.

Many consider exercise testing to be contraindicated in pediatric patients with severe AS in whom surgical or transcatheter intervention is clearly warranted [5]. These patients are at increased risk for sudden death and other serious complications during exercise [6], and the risks of exercise testing therefore do not outweigh the benefits of the procedure, as the data will have minimal impact upon the patient's management. Consequently, pediatric patients with more than moderate, isolated AS rarely undergo exercise testing. AR or mixed aortic valve disease are, by far, the more common physiologic conditions encountered in the pediatric exercise physiology laboratory.

Exercise Function

The exercise capacity of pediatric patients with aortic valve disease who are referred for exercise testing tends to be remarkably well preserved. (As noted previously, this generalization may not apply to patients with severe AS, as they are not often referred for exercise testing.) In a study of 26 consecutive, asymptomatic patients with moderate or severe AR, Rhodes et al. reported that the peak $\dot{V}_{O2}$ averaged 94 ± 23 %predicted. Only 7/26 had a peak $\dot{V}_{O2}$ less than 75 %predicted. Exercise capacity did not correlate with any of the measured (resting) echocardiographic parameters of ventricular function. However, a low peak $\dot{V}_{O2}$ was almost always associated with a depressed O_2 pulse at peak exercise, suggesting that an inability to maintain forward stroke volume during exercise was the primary factor responsible for the patients' poor exercise function [7]. In a study of 30 patients (median age 13.1 years) who had undergone balloon valvuloplasty for critical or severe AS in early infancy (median age 12 days), peak $\dot{V}_{O2}$ averaged 87 ± 18 %predicted and was above 70 %predicted in all but seven patients. Significant residual aortic valve disease was common in this cohort. The median peak Doppler gradient across the aortic valve was 34 mm Hg (range 0–65 mm Hg) and 37% of the patients had moderate or severe AR. Once again, a low peak $\dot{V}_{O2}$ was almost always associated with a low O_2 pulse. There was a negative correlation between age at testing and peak $\dot{V}_{O2}$. No other demographic, historical, or echocardiographic variables were associated with peak $\dot{V}_{O2}$.

Other studies have also documented that the exercise function of pediatric patients with aortic valve disease tends to be well preserved. Both Goforth et al. [8] in a study of 25 children and Alpert et al. [9], in a study that included 20 pediatric patients with AR, found that the exercise capacity of their patients did not differ from that of normal control subjects. Similarly, Goldberg et al. found that the average relative maximum endurance index of 14 children with AR was only slightly reduced compared to normal subjects, and that the exercise capacity of all but 3 of the subjects was within the normal range [10]. In a recent study of asymptomatic adults (aged 44 ± 14 years), Broch et al. found that peak $\dot{V}_{O2}$ was well preserved (107 ± 26 %predicted), and that patients with a lower resting heart rate and larger LV end diastolic volume (based on cardiac

MRI measurements) tended to have higher peak $\dot{V}_{O2}$. Measurements of the AR fraction at rest did not correlate with peak $\dot{V}_{O2}$ [3].

The well-preserved exercise capacity of most pediatric patients with aortic valve disease attests to the effectiveness of the LV remodeling that is typically encountered in this patient population, and the salutary hemodynamic effects of the decline in SVR that occurs during exercise.

Clinical Implications

In adult patients with AS, exercise-induced ST changes and a blunted systolic blood pressure response to exercise have been shown to be useful in identifying patients with and without an increased risk for sudden death [11, 12]. These phenomena are commonly encountered in pediatric patients with aortic valve disease [7, 13, 14] and their prognostic value has not been established. Unless extreme, the clinical significance of these findings in the pediatric age group is probably only marginal. Exercise-induced symptoms [12, 15] and/or complex ventricular arrhythmias have also been associated with an increased risk of sudden death in adult AS patients [11]. These phenomena are rarely encountered in pediatric patients and probably do have important clinical implications. One study has also reported that stress echocardiography can detect wall motion abnormalities in some pediatric patients with AS, but the clinical significance of these observations has not been established [13].

Among pediatric patients, a peak-to-peak systolic gradient of >50 mm Hg, in the absence of significant AR, is considered an indication for balloon valvuloplasty. Surgical intervention is usually required for patients with high systolic gradients and more than mild AR [1]. Decisions about when to refer these patients to surgery can often be extremely difficult. Exercise testing can be a particularly helpful adjunct to the decision-making process in these patients.

In adult patients with chronic, severe AR, aortic valve repair/replacement (AVR) is generally recommended if they are symptomatic, have evidence of ventricular dysfunction (LVEF <50% in the absence of another cause for the LV dysfunction) or severe LV dilation (LV end systolic dimension >50 mm or > 25 mm/m^2) [16, 17]. Among adult patients with chronic severe AR who develop symptoms, a high risk of death has been documented if AVR is not performed. In a series of 246 patients with severe AR followed without surgery, those who were New York Heart Association (NYHA) class III or IV had a mortality rate of 24.6% per year; even NYHA class II symptoms were associated with increased mortality (6.3% per year). Numerous other studies indicate that survival and functional status after AVR are related to severity of preoperative symptoms assessed either subjectively or objectively with exercise testing, with worse outcomes in patients who undergo surgery after development of moderately severe (NYHA class III) symptoms or impaired exercise capacity. Postoperative survival is significantly higher in symptomatic patients with normal LVEF compared with those with impaired systolic function, but even in symptomatic patients with severely depressed systolic function, surgery is recommended over medical therapy. Surgical risks and outcomes are worse in patients who have long-standing (e.g., >14 months) LV dysfunction, independent of the level of symptoms. The importance attached to the LV end systolic dimension relates to the concern that end systolic dilation may be a precursor to or early sign of LV dysfunction. For patients without symptoms, LV dysfunction or severe LV dilation, continued observation and medical management is felt to carry a lower risk than surgical or transcatheter intervention [16, 17]. The value of exercise testing in the objective assessment of the adult AR patient's level of symptoms has been recognized [17]. However, the exact role of exercise testing in the determination of when to intervene in adult patients with AR is not well established [18, 19].

Data regarding the risks and benefits of surgical/transcatheter intervention for pediatric patients with chronic AR are not nearly as robust as the adult data. However, the principles that have been developed for adult patients with regard to symptoms, LV dysfunction, and LV dilation are generally applied; i.e., surgical intervention should be undertaken when there are symptoms or when (or, perhaps, just before!)

evidence of ventricular dysfunction develops. Additional considerations that apply to the pediatric patient include the likelihood that hemodynamic function of a repaired or prosthetic valve will deteriorate more rapidly on account of the rapid somatic growth during the pediatric years, the unattractive option of using anticoagulants in an active child or adolescent with a mechanical prosthetic valve, and the greater likelihood that aortic valve repair, rather than replacement, can be achieved in a pediatric patient compared to an adult with calcific aortic valve disease [1].

Data from exercise physiology testing can help inform the difficult clinical decisions regarding the timing of interventions for pediatric AR (±AS). As noted in Chap. 13, the assessments of "symptoms," which is a crucial component of the decision-making process in these patients, is often unreliable when based upon the reports of a child, his/her parents, or an adult with congenital heart disease. Cardiopulmonary exercise testing (CPET), however, can provide quantitative, objective, and reproducible data in this regard. It is not uncommon to find that patients who are "asymptomatic" in fact have significantly depressed exercise function, or that patients who complain of exercise intolerance actually have normal exercise function. Moreover, as discussed previously, imaging studies performed at rest cannot accurately identify the relatively small subset of pediatric patients with AR who have significantly depressed exercise function. If, however, CPET reveals that a patient's peak $\dot{V}_{O2}$ and the oxygen pulse (i.e., forward stroke volume) at peak exercise are low, concern about early LV dysfunction should be raised and prompt further evaluation, closer monitoring, and/or a lower threshold for surgical intervention considered [7].

CPET is particularly helpful for patients with borderline indications for intervention. If the results of the CPET are reassuring, continued conservative management and close observation is probably reasonable. However, if the CPET elicits concerning findings, such as a low peak $\dot{V}_{O2}$ and peak oxygen pulse, severe ST changes, arrhythmias, hypotension, angina, syncope or near syncope, early intervention would be appropriate. A decline in the oxygen pulse during exercise is an unusual and potentially ominous sign that should also motivate consideration of early intervention.

CPET testing is also worthwhile for asymptomatic AR patients with normal resting LV function and more modest LV dilation. If the CPET abnormalities previously described are detected, or if a significant deterioration is detected on serial CPET studies, the possibility that the patient has been miscategorized on the basis of his/her non-CPET data should be considered. Under these circumstances, it is appropriate to seek additional data, arrange more frequent follow-up and perhaps lower the threshold for intervention.

Prototypical Patient

The patient was a 10-year-old boy who was born with a bicuspid aortic valve. Although there was only mild AS/AR at birth, over time the AR gradually worsened. There was only trivial AS (peak echocardiographic gradient 15 mm Hg). At the time of the exercise test, the AR fraction, by MRI, had increased to 51%. The LV end diastolic volume was 197 ml/m^2, end systolic volume 83 ml/m^2, and ejection fraction 0.58. He was, however, asymptomatic. He was treated with afterload reduction therapy. The CPET (Table 16.1 and Fig. 16.1) was performed to further assess his current cardiologic status.

Table 16.1 Selected data from the cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	55.6
Peak $\dot{V}_{O2}$ (%predicted)	98
Peak work rate (W)	121
Peak work rate (%predicted)	101
Peak RER	1.10
Peak O_2 pulse (%predicted)	99
Peak heart rate (bpm)	200
Peak heart rate (%predicted)	103
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	58
Blood pressure response	Normal
$\dot{V}_E/\dot{V}_{CO2}$ slope	28
End-tidal pCO2 at VAT (mm Hg)	40
End-tidal pCO2 during exercise	Normal

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

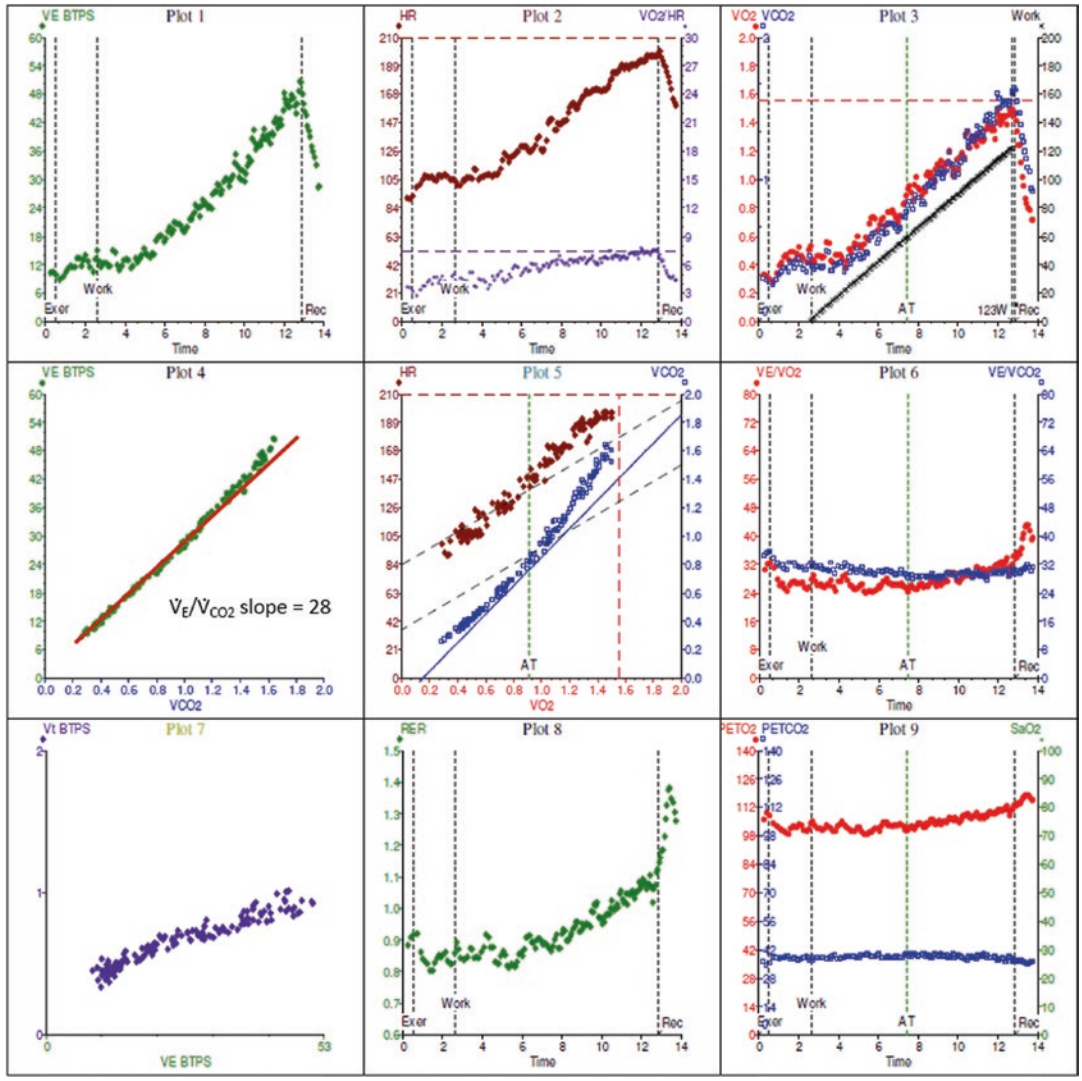


Fig. 16.1 Nine-panel graph from a prototypical patient with aortic regurgitation. Abbreviations: AT ventilator anaerobic threshold; BTPS body temperature and pressure, saturated; Exer exercise; PETCO2 end-tidal pCO2; PETO2 end-tidal pO2; Rec recovery; RER respiratory exchange ratio; $\dot{V}_{CO2}$ carbon dioxide production; $\dot{V}_E$ minute ventilation; $\dot{V}_{O2}$ oxygen consumption; $\dot{V}_{O2}$/HR oxygen pulse

A cycle ergometer with a 12 W/min ramp was employed. The respiratory exchange ratio (RER) at peak exercise was 1.10 and the peak heart rate was 200 bpm, indicating that he expended a good effort. His peak work rate, peak $\dot{V}_{O2}$, peak O_2 pulse and $\dot{V}_{O2}$ at the ventilatory anaerobic threshold (VAT) were normal. No ectopy or significant STT changes developed during the study. His systolic blood pressure increased appropriately during exercise. His gas exchange during exercise was normal. He did not experience any symptoms during the study.

Despite the presence of severe AR at rest, the patient was able to increase his forward stroke volume (as reflected by the O_2 pulse) to appropriate levels at peak exercise, and was thereby able to achieve normal peak exercise parameters. The preserved exercise function probably reflected the fact that: (1) the health of his LV was still quite good, and (2) the systemic vasodilation

associated with exercise probably mitigated the hemodynamic effects of the incompetent aortic valve and reduced the severity of the AR during exercise.

References

1. Keane JF, Fyler DC. Aortic outflow abnormalities. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Saunders Elsevier; 2006. p. 581–602.
2. Litwin SE. Aortic valve disease. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Braunwald E, editors. Braunwanld's heart disease: a textbook of cardiovascular medicine. 11th ed. Philadelphia: Elsevier; 2018.
3. Broch K, Urheim S, Massey R, Stueflotten W, Fossa K, Hopp E, et al. Exercise capacity and peak oxygen consumption in asymptomatic patients with chronic aortic regurgitation. Int J Cardiol. 2016;223:688–92.
4. Stern H, Calvarezos L, Meierhofer C, Steinlechner E, Muller J, Hager A, et al. Physical exercise reduces aortic regurgitation: exercise magnetic resonance imaging. JACC Cardiovasc Imaging. 2014;7(3):314–5.
5. Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, et al. Clinical stress testing in the pediatric age group: a statement from the american heart association council on cardiovascular disease in the young, committee on atherosclerosis, hypertension, and obesity in youth. Circulation. 2006;113(15):1905–20.
6. Keane JF, Driscoll DJ, Gersony WM, Hayes CJ, Kidd L, O'Fallon WM, et al. Second natural history study of congenital heart defects. Results of treatment of patients with aortic valvar stenosis. Circulation. 1993;87(2 Suppl):I16–27.
7. Rhodes J, Fischbach PS, Patel H, Hijazi ZM. Factors affecting the exercise capacity of pediatric patients with aortic regurgitation. Pediatr Cardiol. 2000;21(4):328–33.
8. Goforth D, James FW, Kaplan S, Donner R, Mays W. Maximal exercise in children with aortic regurgitation: an adjunct to noninvasive assessment of disease severity. Am Heart J. 1984;108(5):1306–11.
9. Alpert BS, Moes DM, Durant RH, Strong WB, Flood NL. Hemodynamic responses to ergometer exercise in children and young adults with left ventricular pressure or volume overload. Am J Cardiol. 1983;52(5):563–7.
10. Goldberg SJ, Mendes F, Hurwitz R. Maximal exercise capability of children as a function of specific cardiac defects. Am J Cardiol. 1969;23(3):349–53.
11. Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. Heart. 2001;86(4):381–6.
12. Alborino D, Hoffmann JL, Fournet PC, Bloch A. Value of exercise testing to evaluate the indication for surgery in asymptomatic patients with valvular aortic stenosis. J Heart Valve Dis. 2002;11(2):204–9.
13. Naik R, Kunselman A, Wackerle E, Johnson G, Cyran SE, Chowdhury D. Stress echocardiography: a useful tool for children with aortic stenosis. Pediatr Cardiol. 2013;34(5):1237–43.
14. Mitchell BM, Strasburger JF, Hubbard JE, Wessel HU. Serial exercise performance in children with surgically corrected congenital aortic stenosis. Pediatr Cardiol. 2003;24(4):319–24.
15. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. Eur Heart J. 2005;26(13):1309–13.
16. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al. 2008 focused update incorporated into the acc/aha 2006 guidelines for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association task force on practice guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the society of cardiovascular anesthesiologists, society for cardiovascular angiography and interventions, and society of thoracic surgeons. J Am Coll Cardiol. 2008;52(13):e1–142.
17. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 aha/acc guideline for the management of patients with valvular heart disease: executive summary: a report of the American college of cardiology/American heart association task force on practice guidelines. J Am Coll Cardiol. 2014;63(22):2438–88.
18. Pierard LA, Dulgheru R. Exercise testing and stress imaging in aortic valve disease. Curr Treat Options Cardiovasc Med. 2017;19(7):54.
19. Borer JS. Management decisions in aortic regurgitation: has the time for exercise assessment finally arrived? JACC Cardiovasc Imaging. 2009;2(1):56–7.

Coarctation of the Aorta

17

Jonathan Rhodes and Alexander R. Opotowsky

Basic Anatomy

Coarctation of the aorta (CoA) is characterized by distal aortic arch obstruction. The obstruction is typically located opposite to the entry of the ductus arteriosus ("juxtaductal") and may be just proximal or distal to the left subclavian artery. It is often associated with a variable degree of aortic arch hypoplasia. A bicuspid aortic valve is present in ~50% of cases. Ventricular septal defects, left-sided obstructive lesions, and other intracardiac anomalies are also commonly encountered [1]. Some investigators have also found evidence that CoA is sometimes associated with a more generalized aortopathy [2, 3]. Following repair of CoA, a variable degree of arch obstruction may remain [4, 5]. Aortic compliance may also be abnormal [2, 3, 6, 7].

Hemodynamics

Patients who have had CoA surgery are prone to developing systemic hypertension and the complications related to this condition (e.g., left ventricular hypertrophy, premature atherosclerotic disease, etc.), even after successful repair [3–5, 8–15]. At rest, a small systolic gradient is often detectable across the aortic arch. In the exercise laboratory, this gradient may be detected by obtaining (near) simultaneous right upper and lower extremity blood pressures, or with Doppler echocardiography. Doppler estimates of the arch gradient should correct for the proximal velocity [4, 12, 16]. Occasionally, a patient will have an aberrant right subclavian artery that arises distal to the CoA; under these circumstances, a left upper extremity blood

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

A. R. Opotowsky
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Exercise Physiology Laboratory, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: alexander.opotowsky@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_17

pressure should be determined. Rarely, both the left subclavian artery and the aberrant right subclavian artery arise distal to the CoA. In these cases only Doppler echocardiography can provide reliable estimates of the arch gradient.

Exercise Function

The exercise function of patients with repaired aortic CoA tends to be mildly reduced [11, 14]. Immediately after exercise, dramatic increases in the arch gradient and the systolic pressure proximal to the obstruction are commonly observed [11, 14, 17]. These abnormalities impose a pressure load on the left ventricle. Consequently, the left ventricle's ability to augment stroke volume during exercise may be impaired – a phenomenon reflected by a low oxygen pulse at peak exercise [8, 11, 17]. The residual arch obstruction may also impair blood flow and oxygen delivery to the lower extremities during exercise. The muscles in the legs may therefore develop an early and excessive reliance upon anaerobic metabolism for the generation of the ATP required for exercise. This phenomenon may be reflected by in a disproportionately low anaerobic threshold and/or oxygen consumption/work rate relationship [12]. Consistent with this hypothesis, lower extremity muscle biopsies obtained during exercise from patients who have had CoA repairs have been found to contain higher levels of lactate than did biopsies obtained from normal subjects under similar conditions [18]. Doppler echocardiographic studies have also found that patients with successfully repaired CoA have impaired lower extremity blood flow during exercise [6].

Gas exchange during exercise, as reflected by the $\dot{V}_E/\dot{V}_{CO2}$ slope, tends to be normal [17]. In the absence of beta blocker therapy, the heart rate response to exercise also tends to be normal.

Clinical Implications

Exercise-induced arch gradients and/or upper extremity systolic hypertension have been associated with an increased risk for the development of systemic hypertension and left ventricular hypertrophy [8, 14, 15]. Indeed, compared to the systolic blood pressure at rest, the peak-exercise systolic blood pressure has been found to have a much stronger association with left ventricular hypertrophy [11]. Some investigators have therefore suggested that early anti-hypertensive therapy be considered in patients found to have these abnormalities [4, 15, 16]. However, in the absence of a significant resting gradient and detectable anatomic obstruction, it is unclear whether surgical and/or transcatheter interventions have a role in this clinical setting.

Boston Children's Hospital Experience

Between 2003 and 2017, 720 cardiopulmonary exercise tests were performed on 374 patients with CoA at Boston Children's Hospital (Table 17.1). Patients with complex congenital heart disease diagnosis were excluded, while those with mild concomitant left-sided obstructive lesions or simple defects were not. Of these, 548 were maximal studies as defined by a maximal respiratory exchange ratio >1.09. Age at the time of cardiopulmonary exercise testing (CPET) averaged 27 ± 12 years old, and 46.9% of patients were female. Body mass index (BMI) averaged 24.8, and 16.1% of the patients were obese (BMI > 30 kg/m^2). Most tests (79.0%) were performed by cycle ergometry with the remainder performed using a treadmill. Description of exercise test results is provided in Table 17.1. On average, %predicted peak $\dot{V}_{O2}$ was slightly low, and the oxygen pulse at peak exercise was in the low-normal range. The $\dot{V}_E/\dot{V}_{CO2}$ slope was

Table 17.1 Data from patients with repaired CoA undergoing cardiopulmonary exercise tests at Boston Children's Hospital 2003–2017

	n	Peak $\dot{V}_{O2}$ (% predicted)	Peak $\dot{V}_{O2}$ (mL/kg/min)	Peak HR (bpm)	Peak O_2 Pulse (%predicted)	$\dot{V}E/\dot{V}_{CO2}$ slope	Resting O_2 saturation (%)	Peak O_2 saturation (%)
All	548	82±20	29±9	166±23	90±21	26±5	98±3	98±2
		51/67/80/94/120	15/22/29/35/45	120/153/169/182/196	59/74/86/104/127	20/23/25/28/33	96/98/98/99/100	95/98/98/98/99
≤ 18 years old	143	86±20	35±9	176±20	95±23	27±4	98±2	98±2
		54/71/83/100/122	21/29/34/41/49	134/168/180/190/200	65/77/92/110/132	20/24/27/29/35	98/98/99/99/100	97/98/98/98/99
19–30 years old	229	76±17	29±8	168±21	84±18	26±5	98±3	98±2
		49/63/75/87/107	17/22/28/34/43	129/157/171/184/196	57/72/81/94/117	20/23/25/27/34	96/98/98/99/100	96/98/98/99/99
> 30 years old	176	86±23	25±9	154±23	94±23	25±4	98±2	97±2
		51/67/86/100/123	14/18/24/31/44	113/139/160/169/185	56/77/94/109/129	20/23/25/27/32	96/98/98/99/99	93/97/98/98/99

Data are presented as mean±SD with $^{5\text{-}25\text{-}50\text{-}75\text{-}95^{th}}$ percentiles in the row directly below
HR heart rate, *bpm* beats per minute

normal in the vast majority of patients. Hypoxemia was rare. Peak $\dot{V}_{O2}$ indexed to body mass declined steadily with age. Patients with CoA, on average, had elevated resting upper extremity blood pressure (systolic blood pressure ~7 mm Hg higher than patients referred for exercise testing who do not have CoA, 125 vs. 118 mm Hg) and peak exercise blood pressure (~23 mm Hg higher peak systolic blood pressure, 170 vs. 147 mm Hg; Fig. 17.1). Peak systolic blood pressure >200 mm Hg during a maximal test was observed in 19.1% of patients with CoA compared with 1.7% of those without CoA.

Prototypical Patient

This was a 19-year-old man who underwent surgical repair of a severe coarctation of the aorta when he was 4 days old. He subsequently had three balloon angioplasty procedures for recurrent coarctation. A cycle (25 W/min) cardiopulmonary exercise test (Table 17.2 and Fig. 17.2) was obtained to better characterize and understand his current physiologic status. At the time of the test, he had no significant cardiologic symptoms. He reported that he "worked out regularly" without difficulty. His physical examination and echocardiogram were consistent with no more than mild residual aortic arch obstruction.

Based upon his peak respiratory exchange ratio (RER) and his peak heart rate, the patient expended a good effort. His peak work rate was normal. The peak $\dot{V}_{O2}$ was borderline-low. The $\dot{V}_{O2}$ at the ventilatory anaerobic threshold (VAT) was quite low. The $\Delta\dot{V}_{O2}/\Delta$Work Rate was also low. Gas exchange during exercise was normal. His baseline blood pressure was normal and there was no gradient between his right arm and leg. Immediately post-exercise, mild systolic

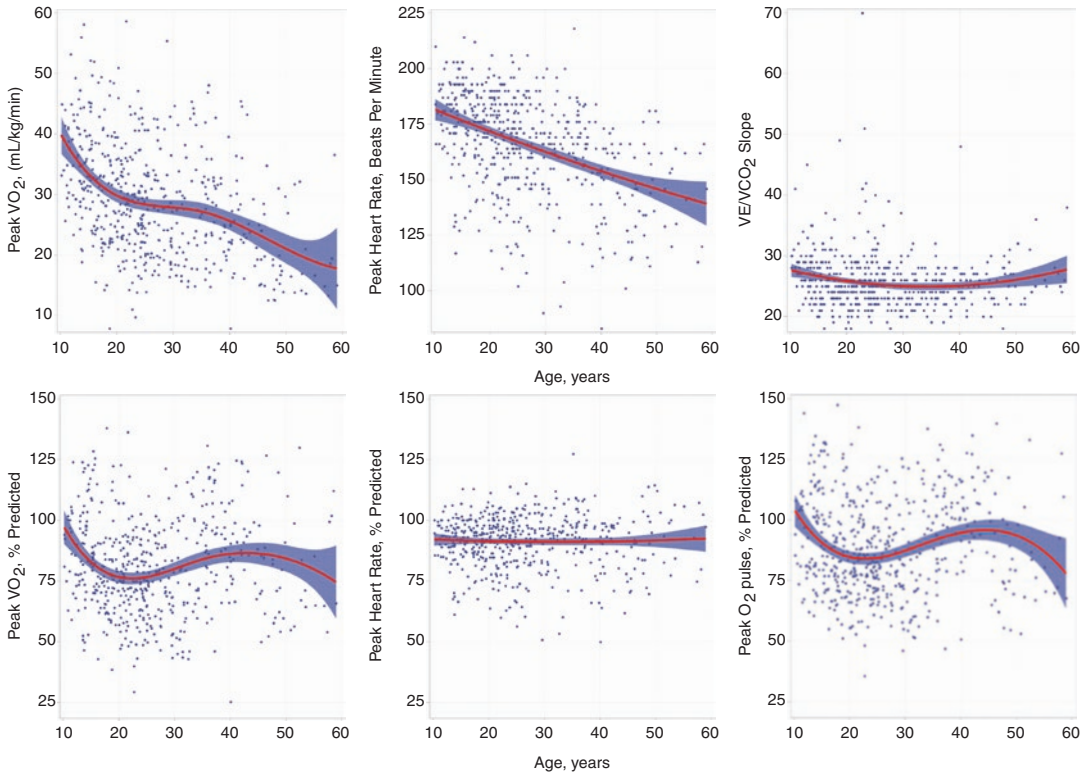


Fig. 17.1 Cardiopulmonary exercise test findings in patients with coarctation of the aorta who completed a maximal (respiratory exchange ratio >1.09) exercise test at Boston Children's Hospital between 2003 and 2017. Each point represents data for a single cardiopulmonary exercise test. The red line represents a restricted cubic spline fit to the data, with 95% confidence limits for the best fit line in semi-transparent blue. Only data for patients 10–60 years old with values between 20% and 150% predicted are presented

Table 17.2 Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	34.8
Peak $\dot{V}_{O2}$ (% predicted)	84
Peak work rate (W)	226
Peak work rate (% predicted)	107
Peak RER	1.35
Peak O_2 pulse (% predicted)	88
Peak heart rate (bpm)	176
Peak heart rate (% predicted)	95
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	28
$\Delta\dot{V}_{O2}/\Delta$work rate (ml/min/W)	8.3
$\dot{V}_E/\dot{V}_{CO2}$ slope	23
Right arm systolic pressure, rest (mm Hg)	122
Left leg systolic pressure, rest (mm Hg)	131
Right arm systolic pressure, post-exercise (mm Hg)	210
Left leg systolic pressure, post-exercise (mm Hg)	129

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

hypertension and > 70 mm Hg gradient were present. The patient did not develop significant symptoms, ectopy, or ST changes during exercise.

The hypertensive response to exercise and the upper-lower extremity systolic blood pressure gradient immediately post-exercise suggest that there were residual aortic arch abnormalities that were not reflected by the patient's baseline physiology. The low $\Delta\dot{V}_{O2}/\Delta$Work Rate and the low VAT probably reflect the fact that blood flow (and oxygen delivery) to the legs was limited during exercise, secondary to the residual aortic arch abnormalities. The leg muscles therefore had to rely upon anaerobic metabolism to generate a greater-than-normal fraction of the ATP required for exercise.

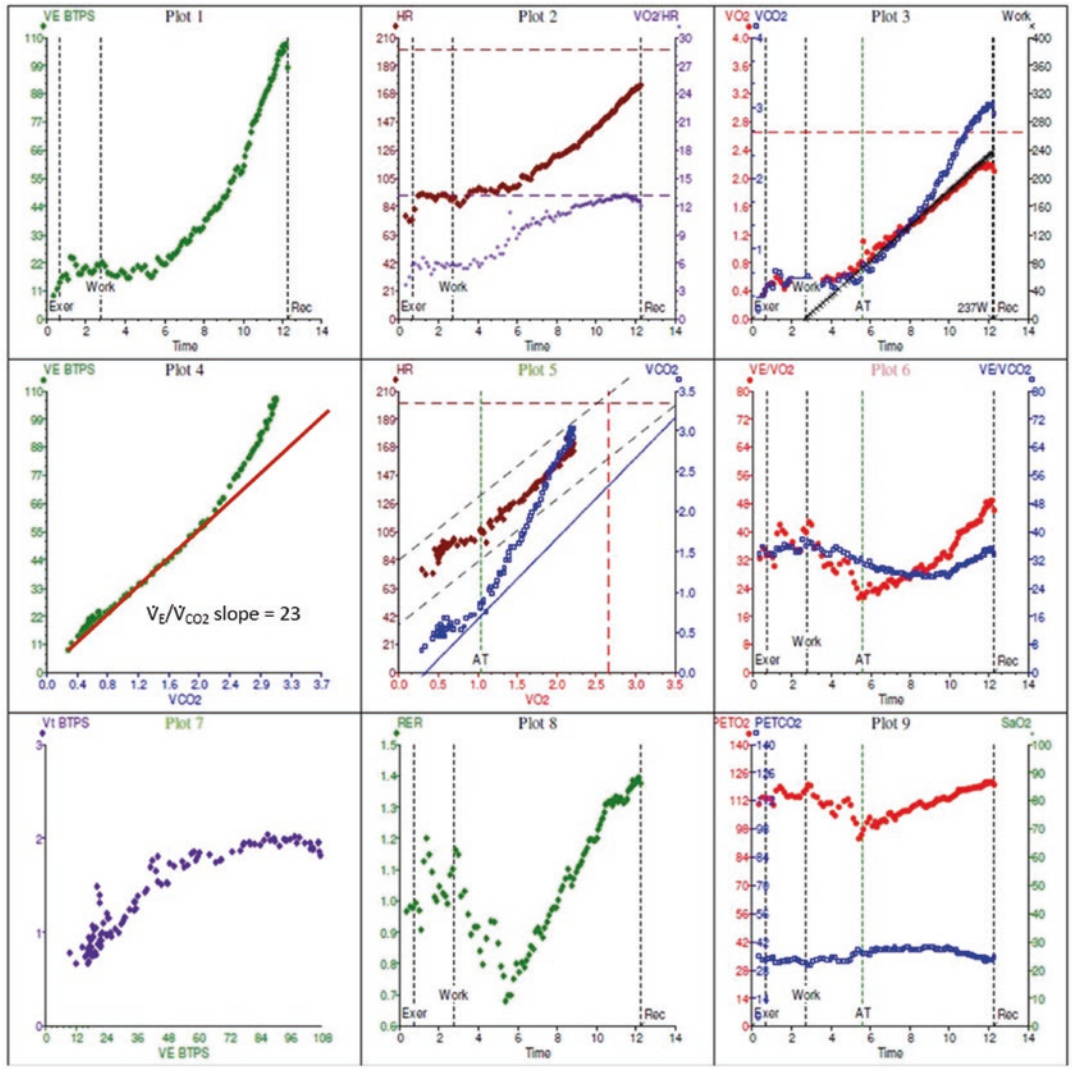


Fig. 17.2 Cardiopulmonary exercise test data on a prototypical patient with repaired coarctation of the aorta. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, PETCO2 end tidal pCO2, PETO2 end tidal pO2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, $\dot{V}_{O2}$ oxygen consumption, $\dot{V}_{O2}$/HR oxygen pulse

References

1. Keane JF, Fyler DC. Coarctation of the aorta. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Elsevier; 2006. p. 627–44.
2. Ong CM, Canter CE, Gutierrez FR, Sekarski DR, Goldring DR. Increased stiffness and persistent narrowing of the aorta after successful repair of coarctation of the aorta: relationship to left ventricular mass and blood pressure at rest and with exercise. Am Heart J. 1992;123(6):1594–600.
3. Canniffe C, Ou P, Walsh K, Bonnet D, Celermajer D. Hypertension after repair of aortic coarctation – a systematic review. Int J Cardiol. 2013;167(6):2456–61.
4. Kimball TR, Reynolds JM, Mays WA, Khoury P, Claytor RP, Daniels SR. Persistent hyperdynamic cardiovascular state at rest and during exercise in children after successful repair of coarctation of the aorta. J Am Coll Cardiol. 1994;24(1):194–200.
5. Freed MD, Rocchini A, Rosenthal A, Nadas AS, Castaneda AR. Exercise-induced hypertension after surgical repair of coarctation of the aorta. Am J Cardiol. 1979;43(2):253–8.

6. Johnson D, Bonnin P, Perrault H, Marchand T, Vobecky SJ, Fournier A, et al. Peripheral blood flow responses to exercise after successful correction of coarctation of the aorta. J Am Coll Cardiol. 1995;26(7):1719–24.
7. Senzaki H, Iwamoto Y, Ishido H, Masutani S, Taketazu M, Kobayashi T, et al. Ventricular-vascular stiffening in patients with repaired coarctation of aorta: integrated pathophysiology of hypertension. Circulation. 2008;118(14 Suppl):S191–8.
8. Buys R, Van De Bruaene A, Muller J, Hager A, Khambadkone S, Giardini A, et al. Usefulness of cardiopulmonary exercise testing to predict the development of arterial hypertension in adult patients with repaired isolated coarctation of the aorta. Int J Cardiol. 2013;168(3):2037–41.
9. Hauser M. Exercise blood pressure in congenital heart disease and in patients after coarctation repair. Heart. 2003;89(2):125–6.
10. Hauser M, Kuehn A, Wilson N. Abnormal responses for blood pressure in children and adults with surgically corrected aortic coarctation. Cardiol Young. 2000;10(4):353–7.
11. Krieger EV, Clair M, Opotowsky AR, Landzberg MJ, Rhodes J, Powell AJ, et al. Correlation of exercise response in repaired coarctation of the aorta to left ventricular mass and geometry. Am J Cardiol. 2013;111(3):406–11.
12. Rhodes J, Geggel RL, Marx GR, Bevilacqua L, Dambach YB, Hijazi ZM. Excessive anaerobic metabolism during exercise after repair of aortic coarctation. J Pediatr. 1997;131(2):210–4.
13. Ruttenberg HD. Pre- and postoperative exercise testing of the child with coarctation of the aorta. Pediatr Cardiol. 1999;20(1):33–7.
14. Trojnarska O, Gwizdala A, Katarzynska A, Lanocha M, Katarzynski S, Oko-Sarnowska Z, et al. Cardiopulmonary exercise test in the evaluation of exercise capacity, arterial hypertension, and degree of descending aorta stenosis in adults after repair of coarctation of the aorta. Cardiol J. 2007;14(1):76–82.
15. Luijendijk P, Bouma BJ, Vriend JW, Vliegen HW, Groenink M, Mulder BJ. Usefulness of exercise-induced hypertension as predictor of chronic hypertension in adults after operative therapy for aortic isthmic coarctation in childhood. Am J Cardiol. 2011;108(3):435–9.
16. Cyran SE. Coarctation of the aorta in the adolescent and adult: echocardiographic evaluation prior to and following surgical repair. Echocardiography. 1993;10(5):553–63.
17. Buys R, Cornelissen V, Van De Bruaene A, Stevens A, Coeckelberghs E, Onkelinx S, et al. Measures of exercise capacity in adults with congenital heart disease. Int J Cardiol. 2011;153(1):26–30.
18. Eriksson BO, Friberg LG, Hanson E, Mellgren G. Comparisons of muscle substrate levels, muscle enzyme activities and muscle morphology in arm and leg muscles in normal subjects and in patients operated upon for coarctation of the aorta in childhood. Scand J Clin Lab Invest. 1981;41(7):695–9.

18 Systemic Right Ventricles with a Biventricular Circulation (L-Transposition and D-Transposition After Atrial Switch Operation)

Alexander R. Opotowsky

Anatomy

In transposition of the great arteries (TGA), there are discordant ventriculoarterial alignments, with the great vessels arising abnormally from the "wrong" ventricle. As a result, the right ventricle ejects to the aorta and the left ventricle ejects to the pulmonary artery. This can occur in the context of various congenital heart defects, most commonly either D-looped transposition of the great arteries (d-TGA) or physiologically corrected transposition of the great arteries (also referred to as congenitally corrected or L-looped; l-TGA). Both forms of TGA can be associated with other congenital heart defects including ventricular septal defects, outflow tract obstruction, atrioventricular canal defects, and coarctation of the aorta.

A. R. Opotowsky (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Exercise Physiology Laboratory, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: alexander.opotowsky@cardio.chboston.org

D-Looped Transposition of the Great Arteries

In the absence of adequate mixing between the deoxygenated and oxygenated circulations, d-TGA is fatal in early life. In the contemporary era, a vast majority of neonates with d-TGA undergo the arterial switch operation, resulting in a systemic left ventricle (see Chap. 19). However, from the 1950s until the widespread adoption of the arterial switch procedure in the 1980s, infants with d-TGA usually underwent a palliative procedure to allow sufficient mixing of oxygenated and deoxygenated blood (either a surgical atrial septectomy or balloon atrial septostomy), followed later in life by an atrial switch operation (e.g., Mustard or Senning procedure). These procedures involve creating atrial baffles to direct deoxygenated systemic venous blood to the subpulmonic left ventricle and oxygenated pulmonary venous blood to the sub-systemic right ventricle. Hence, most patients with d-TGA are now adults >30 years of age and are confronting the long-term consequences of their palliative surgeries. In addition to progressive dysfunction/failure of the systemic morphologic right ventricle, the consequences relevant to exercise include the potential for sinus node dysfunction, baffle leaks and stenoses, and atrial arrhythmias.

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_18

L-Looped Transposition of the Great Arteries

Physiologically corrected TGA involves both transposition of the great arteries as well as discordant atrioventricular connections, usually in the setting of l-looping of the ventricles. As a result, the normal pattern of blood flow—i.e., systemic venous return pumped to the lungs and pulmonary venous return pumped to the body—is preserved. However, the sub-pulmonary ventricle is a morphologic left ventricle while the sub-systemic ventricle is a morphologic right ventricle that may, over time, develop progressive dysfunction/failure. Other issues relevant to exercise include increased prevalence of sub-pulmonary left ventricular outflow tract obstruction, systemic tricuspid valve dysfunction, and an abnormal atrioventricular conduction system with a high incidence of complete heart block.

Hemodynamics

There are four key mechanisms by which aerobic capacity is limited in patients with a systemic right ventricle biventricular circulation: (1) right ventricular systolic dysfunction; (2) tricuspid (i.e., systemic atrioventricular) valve regurgitation, (3) chronotropic dysfunction due to sinus node dysfunction and/or conduction disease, and (4) limitation of venous return due to baffle anatomy. The first three mechanisms are commonly encountered in both d-TGA and l-TGA, though the most common reasons for chronotropic impairment differ between diagnoses, as will be discussed later.

The fourth issue, venous limitation, is more specific to patients with d-TGA who have had an atrial switch procedure. A similar pathophysiology may be seen in patients without congenital heart disease who develop venous obstruction, such as subacute thrombosis of an inferior vena cava filter or venous insufficiency of other cause [1, 2]. With the atrial switch operation, however, some degree of "preload limitation" is probably the rule rather than the exception. This phenomenon is probably at least partially responsible for the observation that many patients with d-TGA and atrial baffle repair appear to have a decline in stroke volume with exercise [3–5].

Exercise Function

In both forms of TGA, the presence of a systemic right ventricle is associated with an increased incidence of heart failure, often related to progressive right ventricular systolic dysfunction and/or tricuspid regurgitation. It appears that the anatomy of the right ventricle and tricuspid valve are not well suited for decades of pumping at systemic pressures. The end result of this physiology is progressive congestive heart failure. Cardiopulmonary exercise test findings parallel those seen in any form of heart failure, i.e., reduced peak $\dot{V}_{O2}$ and O_2 pulse [4, 6–11]. Chronotropic impairment, ranging from mild to pacemaker dependence, is also commonly encountered [7]. Of note, however, resting systemic right ventricular geometry and function explain very little of the variability in exercise response between patients [11]. Elevated $\dot{V}_E/\dot{V}_{CO2}$ is also commonly observed as in patients with congestive heart failure of any cause. The primary mechanism is probably pulmonary congestion and pulmonary blood flow maldistribution causing ventilation/perfusion mismatch and increased physiologic dead space. Both an elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and a depressed peak $\dot{V}_{O2}$ have been found to be predictors of mortality in patients with d-TGA who have had an atrial switch procedure [12].

There are also cardiopulmonary exercise test (CPET) findings with particular implications in various forms of TGA. Right-to-left shunting via a baffle leak (or other cause) causes inefficient ventilation in that increased minute ventilation is required to maintain the same P_aCO_2 and eliminate the equivalent volume of CO_2, since a subset of the high CO_2 systemic venous blood is

bypassing the gas exchange function of the lungs. This is manifest on exercise testing as elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 along with, usually mild, hypoxemia (see Chap. 12). Similar abnormalities may also be seen secondary to ventilation/perfusion mismatch and impaired pulmonary gas exchange in the setting of pulmonary venous baffle obstruction or pulmonary vascular disease. Since atrial baffles are not present in l-TGA, oxygen desaturation, a low end-tidal pCO_2 and an elevated $\dot{V}_E/\dot{V}_{CO2}$ slope may be encountered in the setting of heart failure along with parenchymal lung disease, or another cause of pulmonary venous desaturation. Mild arterial desaturation is also common in patients who have undergone atrial switch procedures, because the coronary sinus blood flow is not usually included in the systemic venous baffle.

Superior vena cava baffle stenosis is relatively common in d-TGA after an atrial switch [13] and may present with effort intolerance related to limited venous return and stroke volume. Other limbs of the atrial baffle system can also become obstructed. Exercise findings include reduced O_2 pulse augmentation. This is not specific for baffle obstruction, however. Even in the absence of anatomic stenosis, the presence of stiff, long, ineffectively contractile atrial baffles impedes augmentation of venous return to each ventricle. This can constitute a major limitation to maximal cardiac output augmentation in this population, as outlined previously. Interestingly, O_2 pulse will sometimes decline with increasing heart rate, especially among patients with rate-responsive pacemakers (Fig. 18.1). In patients without congenital heart disease, this would raise concern for myocardial ischemia or severe systemic ventricular outflow obstruction. However, in this population, it often reflects nothing more than suboptimal atrial baffle dynamics in the population of patients with d-TGA after atrial baffle.

One might wonder why a decline in O_2 pulse is not the usual pattern if the limited invasive data suggest a decline in stroke volume is the norm [3]—a finding also supported by studies

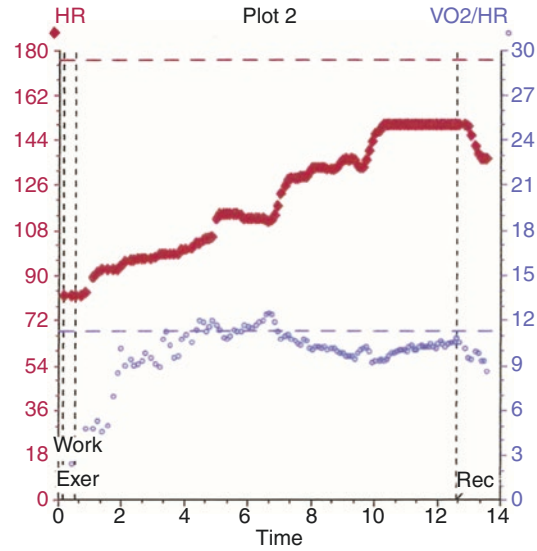


Fig. 18.1 Plot of heart rate (red diamonds, left y-axis) and O_2 pulse (blue open circles, right y-axis) over time during a treadmill cardiopulmonary exercise test in a patient with d-TGA with a Mustard atrial switch. Her course had been complicated by sinus node dysfunction, treated by placement of a pacemaker. There is a pacemaker-mediated increase in heart rate at just before 7 minutes into the test, which is followed by a drop in O_2 pulse—likely due to a decline in stroke volume secondary to the decrease in the time available for ventricular filling at the higher, paced heart rate

that have estimated stroke volume noninvasively [4, 5]. Most likely, patients with d-TGA have a compensatory increase in the capacity of the exercising muscle to extract oxygen from perfusing blood, leading to increased arterial-venous O_2 content difference and low mixed venous oxygen saturation during submaximal exercise [3]. Because O_2 pulse is a function of both stroke volume and the amount of oxygen extracted from each unit of blood, this phenomenon will tend to mitigate the effect of the decline in stroke volume upon the O_2 pulse during submaximal exercise. Near peak exercise, however, the capacity to extract oxygen has achieved a relatively stable maximal level, making the O_2 pulse more sensitive and specific to changes in stroke volume, in the absence of changes in arterial oxygenation.

Myocardial Ischemia

It is challenging to interpret exercise-induced electrocardiogram (EKG) changes in patients with a systemic right ventricle given the universal presence of right ventricular hypertrophy and commonly associated other confounders (e.g., pacemaker, dextrocardia). Stress echocardiography may be useful if heart rate response and images are both sufficient—an unfortunately uncommon situation. Computed tomography (CT) coronary angiography or nuclear perfusion imaging is usually necessary for dependable assessment of ischemia in patients for whom there is at least moderate pretest probability of ischemia. Another challenge is the high reported prevalence of reduced coronary flow reserve and perfusion abnormalities noted among patients with a systemic right ventricle in the absence of obstructive coronary disease or clinical ischemia [14–17].

Of note, dobutamine stress imaging is probably not an equivalent substitute for exercise assessment in the context of d-TGA with atrial baffle repair, as responses in ventricular volumes and thickening and stroke volume vary between these two modalities in this population [18]. There are several possible reasons, such as the entirely distinct impact of these "stresses" on venous return being exposed by the preload limitation imposed by the baffles.

Boston Children's Hospital Experience

Between 2003 and 2017, 519 cardiopulmonary exercise tests were performed at Boston Children's Hospital on 158 patients with d-TGA who had undergone an atrial switch procedure. Of these, 439 were maximal as defined by a maximal respiratory exchange ratio > 1.09. Age at the time of CPET averaged 34 ± 8 years, and 39.6% of patients were female. Body mass index (BMI) averaged 25.9, and 25.9% of the patients were obese (BMI > 30 kg/m^2). Most tests (75.2%) were performed by cycle ergometry with the rest performed using a treadmill. Exercise test results are provided in Table 18.1 and Fig. 18.2. Because this procedure is no longer performed regularly, only eight patients ≤18 years old were tested, and these data are not presented individually.

On average, peak $\dot{V}_{O2}$ is mildly to moderately reduced, with both O_2 pulse and peak heart rate

Table 18.1 Cardiopulmonary test data for patients with d-TGA who have had an atrial level switch operation

	n	Peak $\dot{V}_{O2}$ (%predicted)	Peak $\dot{V}_{O2}$ (mL/kg/min)	Peak HR (bpm)	Peak O_2 Pulse (% predicted)	$\dot{V}_E/\dot{V}_{CO2}$ slope	Resting O_2 saturation (%)	Peak O_2 saturation (%)
All	439	66±16	23±7	152±24	78±19	29±5	97±2	95±4
		40-56-66-77-93	13-18-23-26-35	102-139-153-171-184	51-64-75-88-112	23-26-29-32-40	94-96-97-98-99	89-94-96-97-98
19-30 years old	134	67±14	25±6	159±21	79±18	30±5	97±2	96±2
		45-58-66-75-89	16-22-25-28-38	116-149-166-173-183	55-66-76-89-112	23-26-29-32-40	94-96-98-98-99	92-95-96-97-99
> 30 years old	297	66±16	21±6	149±24	76±18	29±5	97±2	95±4
		39-55-65-77-93	12-17-21-25-33	102-136-151-166-184	49-64-75-86-109	23-26-29-32-37	93-96-97-98-99	89-94-95-97-98

Data are presented as mean ± SD with $_{5}$-$_{25}$-$_{50}$-$_{75}$-$_{95}^{th}$ percentiles in the row directly below
HR heart rate, *bpm* beats per minute

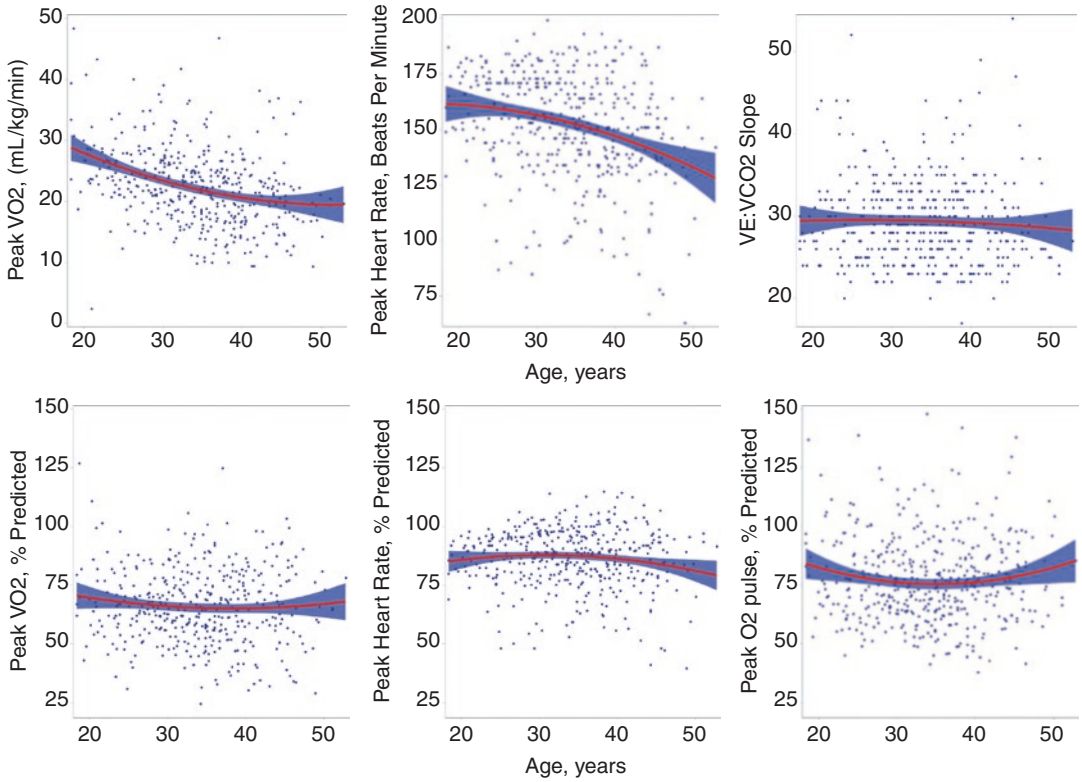


Fig. 18.2 Cardiopulmonary exercise test findings in patients with D-TGA who had undergone an atrial switch procedure who completed a maximal (respiratory exchange ratio >1.09) exercise test at Boston Children's Hospital between 2003 and 2017. Each point represents data for a single cardiopulmonary exercise test. The red line represents a restricted cubic spline fit to the data, with 95% confidence limits for the best fit line in semi-transparent blue. Only data for patients 19–60 years old with values between 20% and 150% predicted are presented

lower than normal. About half of patients have a $\dot{V}_E/\dot{V}_{CO2}$ slope elevated >29. There is a wide range of chronotropic response, and a substantial number of patients have chronotropic incompetence. Note that these data include patients who are paced during exercise.

In our review of arrhythmias during exercise tests performed at Boston Children's Hospital between 2013 and 2015, more than 70% of patients with l-TGA or d-TGA s/p atrial switch procedure developed minor rhythm disturbances. However, in the vast majority of cases, no intervention was required. In only two cases the exercise test was terminated on account of the rhythm disturbance, and no other intervention was required.

A comparison of the data from patients with d-TGA who have undergone atrial vs. arterial switch procedures may be found in Chap. 19.

Prototypical Patient

The patient was a 30-year-old woman who was born with d-TGA and a membranous ventricular septal defect. She underwent a balloon atrial septostomy in the neonatal period and a Senning procedure plus ventricular septal defect repair and patent ductus arteriosus ligation when she was 3.5 months old. She did well postoperatively and was followed thereafter with a degree

Table 18.2 Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	20.1
Peak $\dot{V}_{O2}$ (%predicted)	57
Endurance time (percentile)	<50th
Peak RER	1.13
Peak O2 pulse (%predicted)	64
Peak heart rate (bpm)	169
Peak heart rate (%predicted)	89
Heart rate increase during exercise	Excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	38
Arterial oxygen saturation at peak exercise (%)	98
Arterial oxygen saturation at rest (%)	92
$\dot{V}_E/\dot{V}_{CO2}$ slope	34
End-tidal pCO_2 at VAT (mm Hg)	30
End-tidal pCO_2 during exercise	Low
Blood pressure response	Low-normal

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

of dynamic subpulmonic stenosis. At the time of the CPET, she was asymptomatic, although she did not engage in regular exercise. On the basis of echocardiographic studies, she was thought to have mild-moderate RV dysfunction and was maintained on an angiotensin-converting enzyme inhibitor. No baffle obstruction was detected. The CPET was undertaken to further assess her current cardiopulmonary status. Testing was performed on a treadmill using the standard Bruce protocol (Table 18.2 and Fig. 18.3).

Based upon her peak-exercise respiratory exchange ratio (RER) and peak heart rate, she expended a good effort. Her endurance time, however, was below average, and her peak $\dot{V}_{O2}$ and O_2 pulse were moderately-severely depressed. Indeed, the O_2 pulse appeared to decline at higher levels of exercise. The $\dot{V}_{O2}$ at the ventilatory anaerobic threshold (VAT) was also low, and occurred during the first stage of the Bruce protocol. Although she had a junctional escape rhythm at 52 bpm at rest, sinus rhythm emerged during exercise. The heart rate increase during exercise was, in fact, excessively rapid and her peak heart rate was normal. No other ectopy was detected. Her $\dot{V}_E/\dot{V}_{CO2}$ slope was elevated and her end tidal pCO_2 during exercise was low. She also developed mild arterial desaturation during exercise.

The low O_2 pulse at peak exercise indicates that the patient's poor exercise function was probably due to an inability to increase her stroke volume appropriately during exercise (the mild hypoxemia cannot by itself account for the markedly depressed O_2 pulse, and the patient was not anemic). The low stroke volume may have resulted from the ventricular dysfunction. Systemic (i.e., right) ventricular preload limitation, secondary to the dynamic subpulmonic obstruction and/or the inability of the reconstructed atria/baffles to augment ventricular filling, may also have played a role (this pattern is not infrequent with d-TGA after atrial switch). The excessive heart rate response to exercise may be the result of homeostatic mechanisms (e.g., increased sympathetic tone) responding to the low stroke volume and cardiac output during exercise. The decline in oxygen saturation with exercise may have been due to right-to-left shunting across a small baffle leak. This can also cause elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end tidal pCO_2, as well as ventilation/perfusion mismatch related to the ventricular dysfunction and/or issues with the pulmonary venous baffle. Bradycardia at rest probably reflects sinus node dysfunction in the absence of negative chronotropic medications. The discrepancy between the patient's lack of symptoms and the significantly depressed exercise function documented by formal exercise testing is typical of patients with complex congenital heart disease.

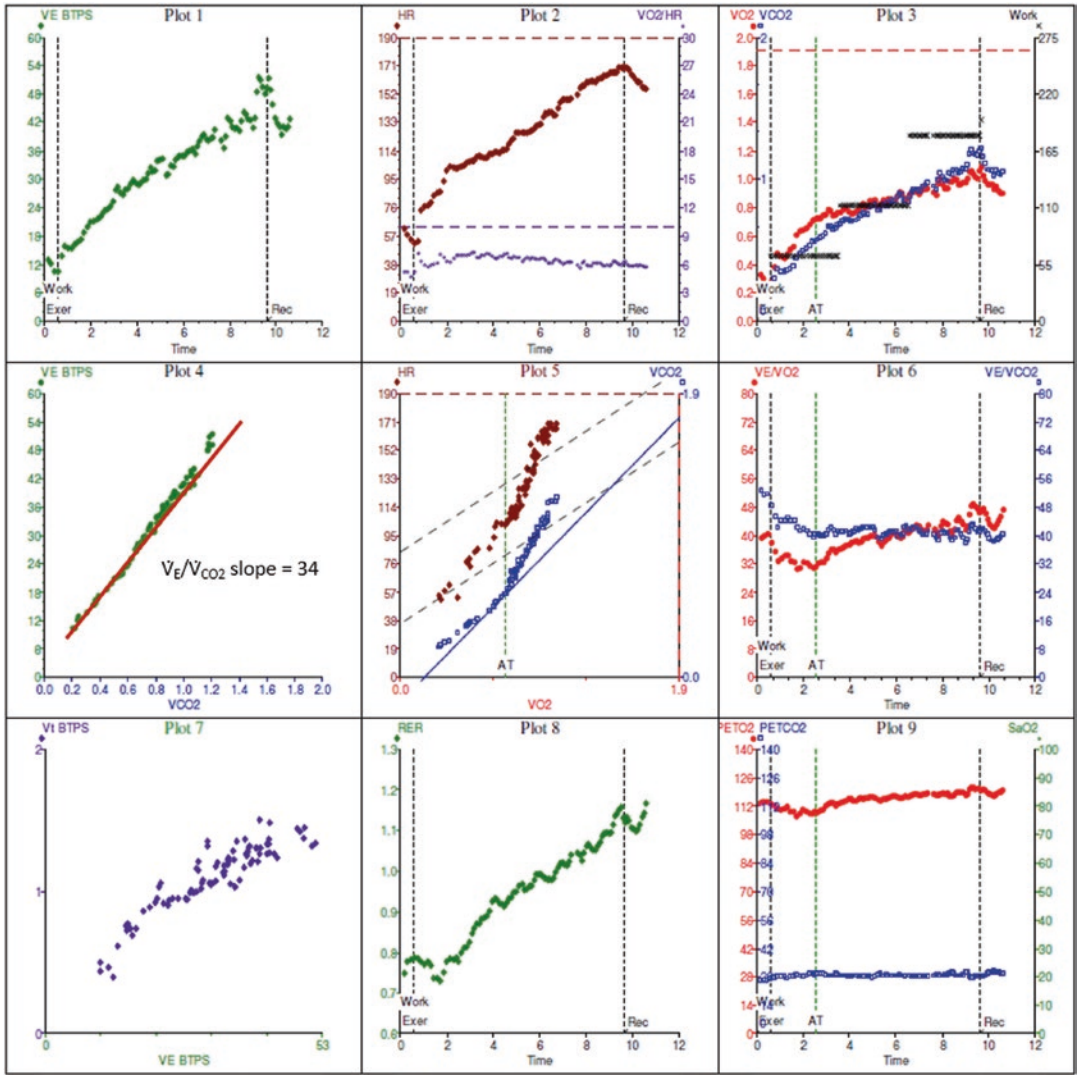


Fig. 18.3 9-panel graph from a prototypical patient with d-TGA s/p atrial switch. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, PETCO2 end tidal pCO2, PETO2 end tidal pO2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, $\dot{V}_{O2}$ oxygen consumption, $\dot{V}_{O2}$/HR oxygen pulse

References

1. Muller TD, Staats BA. Impaired exercise tolerance after inferior vena caval interruption. Chest. 1988;93(4):776–80.
2. Oldham WM, Lewis GD, Opotowsky AR, Waxman AB, Systrom DM. Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing. Pulm Circ. 2016;6(1):55–62.
3. Gilljam T, Eriksson BO, Sixt R. Cardiac output and pulmonary gas exchange at maximal exercise after atrial redirection for complete transposition. Eur Heart J. 1998;19(12):1856–64.
4. Ensing GJ, Heise CT, Driscoll DJ. Cardiovascular response to exercise after the mustard operation for simple and complex transposition of the great vessels. Am J Cardiol. 1988;62(9):617–22.
5. Page E, Perrault H, Flore P, Rossignol A-M, Pironneau S, Rocca C, et al. Cardiac output response to dynamic exercise after atrial switch repair for transposition of the great arteries. Am J Cardiol. 1996;77(10):892–5.
6. Buys R, Budts W, Reybrouck T, Gewillig M, Vanhees L. Serial exercise testing in children, adolescents and young adults with Senning repair for transposi-

tion of the great arteries. BMC Cardiovasc Disord. 2012;12:88.
7. Douard H, Labbe L, Barat JL, Broustet JP, Baudet E, Choussat A. Cardiorespiratory response to exercise after venous switch operation for transposition of the great arteries. Chest. 1997;111(1):23–9.
8. Fredriksen PM, Chen A, Veldtman G, Hechter S, Therrien J, Webb G. Exercise capacity in adult patients with congenitally corrected transposition of the great arteries. Heart. 2001;85(2):191–5.
9. Giardini A, Khambadkone S, Rizzo N, Riley G, Pace NC, Muthialu N, et al. Determinants of exercise capacity after arterial switch operation for transposition of the great arteries. Am J Cardiol. 2009;104(7):1007–12.
10. Reybrouck T, Gewillig M, Dumoulin M, van der Hauwaert LG. Cardiorespiratory exercise performance after Senning operation for transposition of the great arteries. Br Heart J. 1993;70(2):175–9.
11. Shafer KM, Mann N, Hehn R, Ubeda Tikkanen A, Valente AM, Geva T, et al. Relationship between exercise parameters and noninvasive indices of right ventricular function in patients with biventricular circulation and systemic right ventricle. Congenit Heart Dis. 2015;10(5):457–65.
12. Giardini A, Hager A, Lammers AE, Derrick G, Muller J, Diller GP, et al. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. J Am Coll Cardiol. 2009;53(17):1548–55.
13. Moons P, Gewillig M, Sluysmans T, Verhaaren H, Viart P, Massin M, et al. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. Heart. 2004;90(3):307–13.
14. Hornung T, Bernard E, Jaeggi E, Howman-Giles R, Celermajer D, Hawker R. Myocardial perfusion defects and associated systemic ventricular dysfunction in congenitally corrected transposition of the great arteries. Heart. 1998;80(4):322–6.
15. Lubiszewska B, Gosiewska E, Hoffman P, Teresińska A, Różański J, Piotrowski W, et al. Myocardial perfusion and function of the systemic right ventricle in patients after atrial switch procedure for complete transposition: long-term follow-up. J Am Coll Cardiol. 2000;36(4):1365–70.
16. Hauser M, Bengel FM, Hager A, Kuehn A, Nekolla SG, Kaemmerer H, et al. Impaired myocardial blood flow and coronary flow reserve of the anatomical right systemic ventricle in patients with congenitally corrected transposition of the great arteries. Heart. 2003;89(10):1231–5.
17. Singh TP, Humes RA, Muzik O, Kottamasu S, Karpawich PP, Di Carli MF. Myocardial flow reserve in patients with a systemic right ventricle after atrial switch repair. J Am Coll Cardiol. 2001;37(8):2120–5.
18. Oosterhof T, Tulevski II, Roest AAW, Steendijk P, Vliegen HW, van der Wall EE, et al. Disparity between dobutamine stress and physical exercise magnetic resonance imaging in patients with an intra-atrial correction for transposition of the great arteries. J Cardiovasc Magn Reson. 2005;7(2):383–9.

19 D-Transposition s/p Arterial Switch Operation

Jonathan Rhodes and Alexander R. Opotowsky

Basic Anatomy

In d-transposition of the great arteries (d-TGA), the great vessels arise from the wrong side of the ventricular septum; i.e., the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. When an arterial switch operation (ASO) is performed, the great vessels are transected above the sinuses and re-anastomosed to the hemodynamically and anatomically appropriate arterial roots. The coronary arteries are also transferred, along with a "button" of aortic tissue, from the original aortic root to the neoaortic root. The defects in the original aortic root from which the coronary buttons were removed are then patched, usually with autologous pericardium [1].

The mobilization and transfer of the main pulmonary artery can cause stretching/distortion of the branch pulmonary arteries, which sometimes results in significant stenosis of these vessels postoperatively. Kinking and stenosis of the coronary arteries can also complicate the transfer of these vessels. Stenoses can also occasionally develop at any of the sites of surgical anastosmosis [1].

About one-third of patients with d-TGA have additional cardiac defects (e.g., septal defects, outflow tract obstruction, valvular anomalies, aortic coarctation, etc.). When significant, these are usually addressed at the time of the ASO [1].

Hemodynamics

Pulmonary artery stenoses are the most common lesions encountered following the arterial switch procedure. These lesions can cause progressive right ventricular hypertension and pulmonary blood flow maldistribution during exercise. Coronary artery stenosis can cause myocardial ischemia during exercise. The valvular and other structural anomalies sometimes associated with d-TGA can also affect the hemodynamic response to exercise.

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

A. R. Opotowsky
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Exercise Physiology Laboratory, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: alexander.opotowsky@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_19

Exercise Function

The ASO is one of the true success stories in pediatric cardiology. Most studies have found that patients who have had ASO have normal, or near-normal, exercise capacity [2–8]. This is especially true among patients who are free from conditions that might adversely affect the stroke volume response to exercise, such as ventricular dysfunction, significant residual pulmonary artery stenosis or valvular dysfunction. Consistent with this observation, variations in the oxygen pulse at peak exercise account for more than 80% of the variation in peak $\dot{V}_{O2}$ in this population [5]. An impaired chronotropic response to exercise is also sometimes encountered following the ASO [5–7]. However, variations in peak heart rate account for only 7% of the variation in peak $\dot{V}_{O2}$ [5].

Patients who have had surgery in the more recent era (post-1993) also tend to have better exercise function than patients who had surgery in an earlier time period, when the ASO was first introduced. This observation is primarily due to an era effect, as serial exercise studies have found that ASO patients tend to have only a small, gradual decline in exercise function over time [5].

Patients with branch pulmonary artery stenosis may have elevated $\dot{V}_E/\dot{V}_{CO2}$ slopes and low end-tidal pCO2 levels during exercise, in a manner analogous to that seen in patients with repaired tetralogy of Fallot (see Chap. 14). However, unlike those patients, the correlation between peak $\dot{V}_{O2}$ and the $\dot{V}_E/\dot{V}_{CO2}$ slope in patients following the ASO is not strong, probably because a coexisting incompetent pulmonary valve is not typically present [5].

Myocardial Ischemia

Exercise-induced ST changes suggestive of ischemia are sometimes encountered in patients following ASO [5]. Fixed myocardial perfusion defects, present on myocardial perfusion scans at rest and at exercise, are also very common following the ASO, and are thought to be due to events at the time of surgery rather than ongoing myocardial ischemia secondary to coronary insufficiency [4, 9]. Significant reversible defects, suggestive of myocardial ischemia, are occasionally encountered. Exercise- induced wall motion abnormalities are also occasionally detected by stress echocardiography. None of these abnormalities have, in isolation, been found to reliably correlate with clinically significant angiographic coronary artery disease [4, 5, 10]. Exercise testing for myocardial ischemia in this population is therefore currently imperfect; clinical suspicion and common sense must guide the evaluation of these patients. Dramatic exercise test abnormalities, especially when associated with symptoms and detectable across multiple testing modalities (e.g., depressed exercise function, exercise-induced ischemic ST changes, reversible perfusion defects, and/or exercise-induced wall motion abnormalities), should certainly raise concern. However, the approach to the asymptomatic ASO patient with reassuring exercise test results should also be influenced by a recent meta-analysis undertaken by van Wijk et al. These investigators gathered data on 8798 patients with 66,450 patient follow-up years. They found only five cases of late (i.e., >5 years postoperative) sudden death; in only two of these cases was sudden cardiac death thought to be likely [11].

Boston Children's Hospital Experience

Between 2003 and 2017, 384 cardiopulmonary exercise tests were performed on 201 patients with d-looped transposition of the great arteries who had undergone an ASO. This group includes patients with simple transposition as well as those with ventricular septal defects and other minor anomalies. Of the studies performed, 295 were maximal as defined by a maximal respiratory exchange ratio >1.09. Age at the time of cardiopulmonary exercise testing (CPET) was 18 ± 5 years old, and 31.5% were female. Body mass index (BMI) averaged 22.6 and only 5.4% of the patients were obese. Most tests (80.3%) were performed by cycle ergometry with the rest performed using a treadmill. Description of exercise test results is provided in Table 19.1 and Fig. 19.1. Because this procedure was not per-

Table 19.1 Data for patients with D-TGA who have had an arterial switch operation

	n	Peak $\dot{V}_{O2}$ (% predicted)	Peak $\dot{V}_{O2}$ (mL/kg/min)	Peak HR (bpm)	Peak O_2 Pulse (% predicted)	$\dot{V}_E/\dot{V}_{CO2}$ slope	Resting O_2 saturation (%)	Peak O_2 saturation (%)
All	295	82±16	33±8	174±18	90±17	26±4	98±1	98±1
		57-71-82-93-109	20-27-33-39-46	142-165-176-187-200	63-78-89-100-118	21-24-26-28-32	97-98-98-99-100	95-98-98-98-99
≤ 18 years old	151	87±16	35±7	179±13	94±18	27±4	98±1	98±1
		59-76-86-97-118	24-30-35-40-47	153-171-180-190-201	66-81-93-105-125	21-24-26-29-33	97-98-99-99-100	95-98-98-99-100
19-30 years old	141	77±15	31±8	169±20	85±15	26±4	98±1	98±1
		49-67-78-89-104	19-25-30-37-45	130-160-173-181-193	61-76-87-94-111	20-24-25-27-31	97-98-98-99-100	95-98-98-98-99

Data are presented as mean ± SD with $_{5}$-$_{25}$-$_{50}$-$_{75}$-$_{95}^{th}$ percentiles in the row directly below
HR heart rate, *bpm* beats per minute

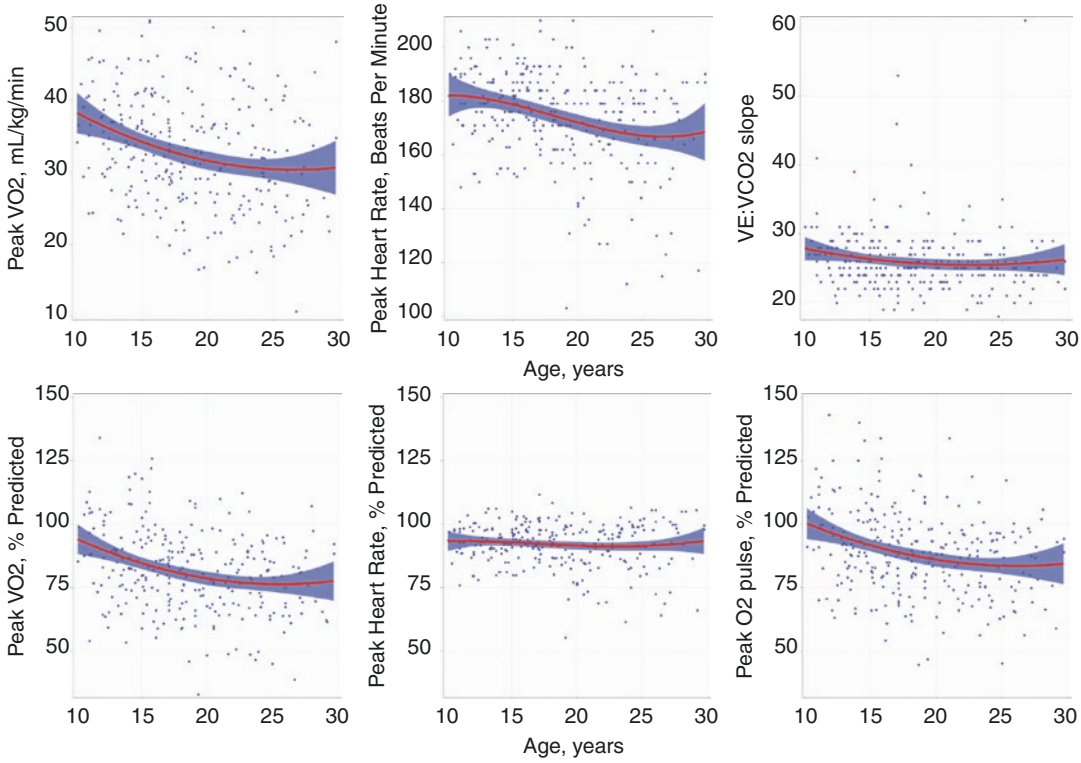


Fig. 19.1 Cardiopulmonary exercise test findings in patients with d-TGA who had undergone an ASO procedure who completed a maximal (respiratory exchange ratio >1.09) exercise test at Boston Children's Hospital between 2003 and 2017. Each point represents data for a single cardiopulmonary exercise test. The red line represents a restricted cubic spline fit to the data, with 95% confidence limits for the best fit line in semi-transparent blue. Only data for patients 19–60 years old with values between 20% and 150% predicted are presented

formed until the past 3–4 decades, only three patients >30 years old were tested, and these data are not presented individually. On average, peak $\dot{V}_{O2}$ was in the normal range (albeit on the low end of normal), with low-normal peak O_2 pulse and peak heart rate. $\dot{V}_E/\dot{V}_{CO2}$ slope was normal in the vast majority. In those with elevated $\dot{V}_E/\dot{V}_{CO2}$ slopes, pulmonary blood flow maldistribution, secondary to residual pulmonary artery stenoses, was probably present. Patients >18 years old tended to have slightly depressed peak $\dot{V}_{O2}$. Based upon a previous analysis, this observation is probably due primarily to an era effect, as the time-related decline in patients who had serial CPET studies was quite small [5].

It is instructive to compare the exercise function of patients who have undergone an ASO with those who have had atrial switch procedures. The % predicted peak $\dot{V}_{O2}$ of the ASO patients was significantly superior, even when patients of the same age range (i.e., 19–30 years of age) were compared. A higher O_2 pulse at peak exercise accounted for most of the discrepancy. The ASO patients were also able to achieve a higher peak heart rate. Patients who had an atrial switch procedure were more likely to have an elevated $\dot{V}_E/\dot{V}_{CO2}$ slope, and also tended to have slightly lower arterial oxygen saturations, especially at peak exercise.

Prototypical Patient

The patient was a 14-year-old adolescent with d-TGA who had an arterial switch procedure when she was 2 days old. She did well postoperatively and was currently asymptomatic except for mild, non-specific chest pain and mild exercise intolerance/dyspnea on exertion. A CPET was obtained to assess her symptoms and current cardiopulmonary status.

The test was performed on a cycle ergometer with a 20 W/min ramp (Table 19.2 and Fig. 19.2).

Table 19.2 Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	30.8
Peak $\dot{V}_{O2}$ (%predicted)	119
Peak work rate (W)	141
Peak work rate (%predicted)	121
Peak RER	1.15
Peak O2 pulse (%predicted)	126
Peak heart rate (bpm)	181
Peak heart rate (%predicted)	95
Heart rate increase during exercise	Appropriate
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	69
Δ(Delta)$\dot{V}_{O2}/\Delta$(Delta)work rate (ml/min/W)	10.1
Blood pressure response	Normal
V_E/V_{CO2} slope	23
End tidal pCO2 during exercise	Normal
Breathing reserve (%)	63
Pre-exercise spirometry	Normal
Post-exercise spirometry	Normal

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

Her peak work rate, peak $\dot{V}_{O2}$, peak heart rate and O_2 pulse at peak exercise were all normal. Her weight-normalized peak $\dot{V}_{O2}$ was slightly low due to her somewhat overweight body habitus (BMI 26.5; 94th percentile). Her gas exchange during exercise was normal. No STT changes or arrhythmias were detected. Her ventricular function was normal at rest and immediately post-exercise. No exercise-induced wall motion abnormalities were detected.

The results of the study were reassuring to the patient, her parents, and the referring clinician. This case may also illustrate the commonly observed discrepancy between a patient's subjective symptoms and objective CPET measurements, although the patient's weight could also have affected her tolerance of weight-bearing physical activities. This phenomenon may have been observed if a treadmill, rather than a cycle, protocol had been employed.

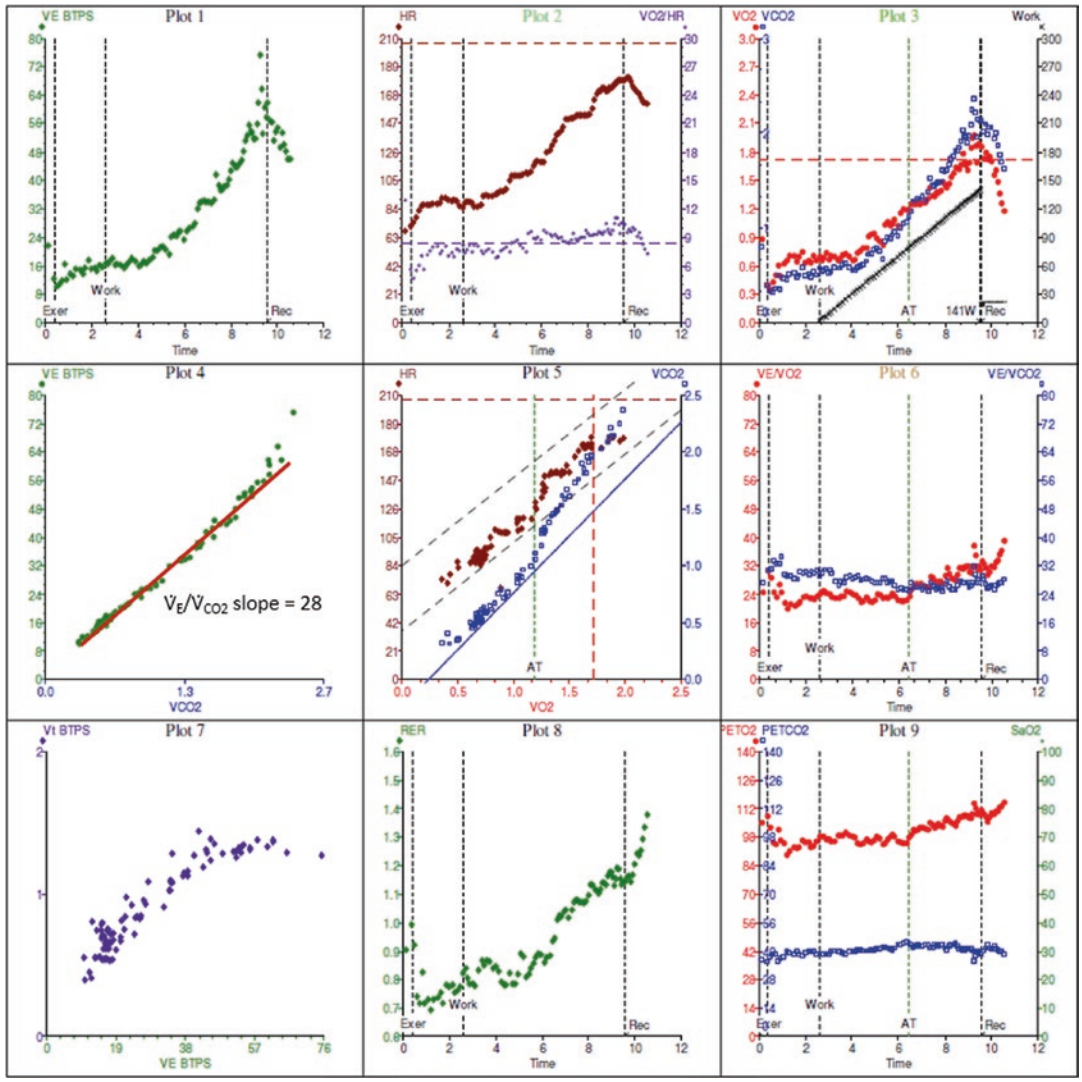


Fig. 19.2 Results of CPET from prototypical patient with d-TGA s/p ASO procedure. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, PETCO2 end tidal pCO2, PETO2 end tidal pO2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, $\dot{V}_{O2}$ oxygen consumption, $\dot{V}_{O2}$/HR oxygen pulse

References

1. Fulton DR, Fyler DC. D-transposition of the great arteries. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Saunders; 2006. p. 645–62.
2. Giardini A, Khambadkone S, Rizzo N, Riley G, Pace NC, Muthialu N, et al. Determinants of exercise capacity after arterial switch operation for transposition of the great arteries. Am J Cardiol. 2009;104(7):1007–12.
3. Mahle WT, McBride MG, Paridon SM. Exercise performance after the arterial switch operation for d-transposition of the great arteries. Am J Cardiol. 2001;87(6):753–8.
4. Weindling SN, Wernovsky G, Colan SD, Parker JA, Boutin C, Mone SM, et al. Myocardial perfusion, function and exercise tolerance after the arterial switch operation. J Am Coll Cardiol. 1994;23(2):424–33.

5. Kuebler JD, Chen MH, Alexander ME, Rhodes J. Exercise performance in patients with d-loop transposition of the great arteries after arterial switch operation: long-term outcomes and longitudinal assessment. Pediatr Cardiol. 2016;37(2):283–9.
6. Samos F, Fuenmayor G, Hossri C, Elias P, Ponce L, Souza R, et al. Exercise capacity long-term after arterial switch operation for transposition of the great arteries. Congenit Heart Dis. 2016;11(2):155–9.
7. Pasquali SK, Marino BS, McBride MG, Wernovsky G, Paridon SM. Coronary artery pattern and age impact exercise performance late after the arterial switch operation. J Thorac Cardiovasc Surg. 2007 Nov;134(5):1207–12.
8. Ruys TP, van der Bosch AE, Cuypers JA, Witsenburg M, Helbing WA, Bogers AJ, et al. Long-term outcome and quality of life after arterial switch operation: a prospective study with a historical comparison. Congenit Heart Dis. 2013;8(3):203–10.
9. Hayes AM, Baker EJ, Kakadeker A, Parsons JM, Martin RP, Radley-Smith R, et al. Influence of anatomic correction for transposition of the great arteries on myocardial perfusion: radionuclide imaging with technetium-99m 2-methoxy isobutyl isonitrile. J Am Coll Cardiol. 1994;24(3):769–77.
10. Legendre A, Losay J, Touchot-Kone A, Serraf A, Belli E, Piot JD, et al. Coronary events after arterial switch operation for transposition of the great arteries. Circulation. 2003;108(Suppl 1):II186–90.
11. van Wijk SWH, van der Stelt F, Ter Heide H, Schoof PH, Doevendans P, Meijboom FJ, et al. Sudden death due to coronary artery lesions long-term after the arterial switch operation: a systematic review. Can J Cardiol. 2017;33(9):1180–7.

Ebstein's Anomaly

20

Jonathan Rhodes and Alexander R. Opotowsky

Basic Anatomy

Ebstein's anomaly is characterized by a variable degree of apical displacement of the septal and posterior leaflets of the tricuspid valve. The leaflets are adherent to the ventricular septum and the portion of the right ventricle (RV) above the adherent leaflets is very thin or "atrialized." The anterior leaflet is also typically elongated and redundant, and the "true" tricuspid valve annulus (i.e., at the anatomic atrioventricular junction) is dilated [1]. These deformities result in a variable degree of tricuspid regurgitation, tricuspid stenosis, and right ventricular dysfunction. An atrial septal defect or patent foramen ovale is almost always present. Abnormalities of the pulmonary valve may also exist. Wolff-Parkinson-White syndrome is present in 10–25% of patients [1, 2]. The tricuspid regurgitation causes (sometimes massive) dilation and fibrosis of the right atrium and atrialized RV [3].

Hemodynamics

The dysfunction of the tricuspid valve and right ventricle that results from this anomaly causes the right atrial pressure to be elevated and may render the right ventricle incapable of maintaining adequate cardiac output. In the presence of an atrial communication, right-to-left atrial shunting will develop with consequent systemic arterial desaturation. The tricuspid valve function tends to deteriorate over time, resulting in progressive tricuspid regurgitation and right atrial dilation and predisposing the patients to atrial arrhythmias. Accessory pathways may complicate arrhythmia management [1, 2]. Left ventricle (LV) dysfunction, either secondary to adverse ventricular-ventricular interactions or intrinsic LV pathology is also sometimes encountered [4, 5].

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

A. R. Opotowsky
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Exercise Physiology Laboratory, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: alexander.opotowsky@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_20

Exercise Function

The exercise function of patients with Ebstein's anomaly varies widely. In a study of 11 asymptomatic children age 6–17 years, Lupoglazoff et al. found peak $\dot{V}_{O2}$ to average 83.3 ± 14.5%predicted. Radojevic et al. studied 51 patients 37.8 ± 13.6 years of age and found a peak $\dot{V}_{O2}$ of 63.2 ± 18.7%predicted. In a study of 21 adult subjects age 24–63 years contrast, Trojnarska et al. reported that peak $\dot{V}_{O2}$ averaged 59.1 ± 12.3%predicted. The impression conveyed by these cross-sectional studies that there is an age-related decline in exercise function was confirmed by a longitudinal study undertaken by Kipps et al. They reported that the baseline peak $\dot{V}_{O2}$ of 23 Ebstein's anomaly patients with serial exercise tests (median age at first exercise test 17.9 years; range 8.1–52.5 years) was 80.2 ± 18.2%predicted. Over a median time interval of 3.3 years (range 0.6–7.3 years), a 1.9 ± 8.0 percentage point per year decline in %predicted peak $\dot{V}_{O2}$ was observed. As with Fontan patients, the decline in %predicted peak $\dot{V}_{O2}$ was steepest among patients less than 18 years of age (3.04 ± 6.78 percentage points/year); thereafter, it was much more gradual (0.43 ± 8.79 percentage points/year). The decline in peak $\dot{V}_{O2}$ was associated with a decline in the oxygen pulse at peak exercise and a small, but statistically significant decline in resting oxygen saturation. On multivariate analysis, however, only a decline in the peak oxygen pulse and a decline in the %predicted peak heart rate were associated with the decline in %predicted peak $\dot{V}_{O2}$. Moreover, the decline in peak O_2 pulse accounted for 77% of the variation in the time-related decline in %predicted peak $\dot{V}_{O2}$ (and 44% of the variation in the time-related decline in the mathematically unrelated %predicted peak work rate).

Muller et al. also reported a progressive decline in the exercise function of patients with unoperated Ebstein's anomaly. Surgical intervention appeared to have a salutary effect upon exercise function [6].

These observations suggest that the deterioration in exercise function is due to a time-related decline in the RV's ability to augment stroke volume during exercise. It seems that, although the chronic volume overload imposed upon the RV by the incompetent tricuspid valve may be relatively well tolerated during childhood, it almost inevitably leads to progressive RV dysfunction. This in turn can cause further RV dilation, further impair tricuspid valve leaflet coaptation, exacerbate tricuspid insufficiency, and further compromise the RV's ability to augment forward stroke volume during exercise.

In patients with an atrial communication, right-to-left shunting may be present, resulting in a degree of arterial desaturation. Right-to-left shunting may increase during exercise if the right ventricle cannot accommodate the hemodynamic demands of exercise and progressive arterial desaturation may develop. Moreover, during exercise, arterial desaturation will worsen for any degree of right-to-left shunting because peripheral oxygen extraction increases and the saturation of the systemic venous blood returning to the heart is lower. Right-to-left shunting will also cause patients to have elevated $\dot{V}_E/\dot{V}_{CO2}$ slopes and lower end-tidal pCO_2 (see Chap. 12). Right-to-left shunting has been associated with a lower exercise capacity [4, 7].

A low peak $\dot{V}_{O2}$ has been found to have ominous prognostic implications. Radojevic et al. reported that a peak $\dot{V}_{O2}$ less than 60% of predicted values is associated with a higher risk for death, non-elective hospitalization, or surgical repair [4].

Kipps et al. also studied the relationship between exercise function and measurements derived from imaging studies. Surprisingly, %predicted peak $\dot{V}_{O2}$ did not correlate with cardiac magnetic resonance imaging (MRI)-derived measurements of RV ejection fraction, LV ejection fraction, RV end diastolic volume, or tricuspid regurgitation fraction. Others have also found no relationship between tricuspid regurgitation severity and peak $\dot{V}_{O2}$ [4, 7, 8]. However, the "Ebstein Severity Grade" (derived from the

ratio of the cross-sectional area of the right atrium and atrialized portion of the right ventricle divided by the cross-sectional area of the rest of the other cardiac chambers, when imaged from the echocardiographic apical four-chamber view) has been found to correlate with %predicted peak $\dot{V}_{O2}$ [4, 9, 10]. These observations recall other studies that have found that the cardiothoracic ratio on a chest X-ray correlates with exercise capacity [4] and is one of the best predictors of mortality in patients with Ebstein's anomaly [11].

The poor correlation between the RV ejection fraction and peak $\dot{V}_{O2}$ may reflect the inherent difficulty in accurately measuring RV volumes in patients with complex RV anatomy encountered in Ebstein's anomaly. Probably of greater importance is the fact that the incompetent tricuspid valve "unloads" the RV; i.e., it permits the RV to eject blood into the relatively low-pressure right atrium. Consequently, the RV ejection fraction will be relatively well preserved and may not accurately reflect the degree of RV dysfunction. The poor correlation between the (resting) tricuspid regurgitation fraction and the peak $\dot{V}_{O2}$ may be related to the fact that the decline in pulmonary vascular resistance during exercise will tend to promote forward blood flow into the pulmonary arteries and reduce the severity of the tricuspid regurgitation in a manner analogous to that seen in patients with pulmonary regurgitation following repair of tetralogy of Fallot (see Chap. 14).

Clinical Implications

A number of clinically important lessons may be drawn from the studies of exercise function in patients with Ebstein's anomaly. It appears reasonable to conclude that cardiac MRI volumetric measurements should not focus solely on the right and left ventricles. Indeed, much of the pathophysiology of this anomaly is reflected by the size of the right atrium and atrialized portion of the RV. Determination of the volumes of these, often overlooked, components of the cardiac anatomy should be included into the cardiac MRI assessment of patients with Ebstein's anomaly [2, 9].

It should also be noted that patients with Ebstein's anomaly often self-limit and are unaware of the severity of their exercise limitations. In light of the important prognostic implications of exercise function in this population, periodic objective measurements of exercise function constitute an important component of clinical management of these patients [2]. The decision to forego or proceed with surgery requires consideration of multiple factors [12, 13]. However, a peak $\dot{V}_{O2}$ less than 60% predicted, or a peak $\dot{V}_{O2}$ that is on a trajectory toward that threshold, should probably motivate consideration of surgery [4, 12]. On the other hand, for the subset of patients who reach adulthood with well-preserved exercise function, continued observation and medical management may be most appropriate, as the decline in exercise function during adulthood is relatively slow.

Boston Children's Hospital Experience

Between 2003 and 2017, 392 cardiopulmonary exercise tests were performed on 169 patients with Ebstein's anomaly at Boston Children's Hospital. Patients with complex congenital heart disease diagnosis or who underwent cardiac transplantation or a Fontan procedure were excluded while those with concomitant simple defects or who had undergone tricuspid valve surgery were not. Of all the tests, 306 were maximal as defined by a maximal respiratory exchange ratio >1.09 (Fig. 20.1). Age at the time of cardiopulmonary exercise testing (CPET) averaged 26 ± 14 years, and 52.3% of patients were female. Body mass index (BMI) averaged 24.8, and 21.2% of the patients were obese (BMI > 30 kg/m^2). Most tests (78.8%) were performed by cycle ergometry with the rest performed using a tread-

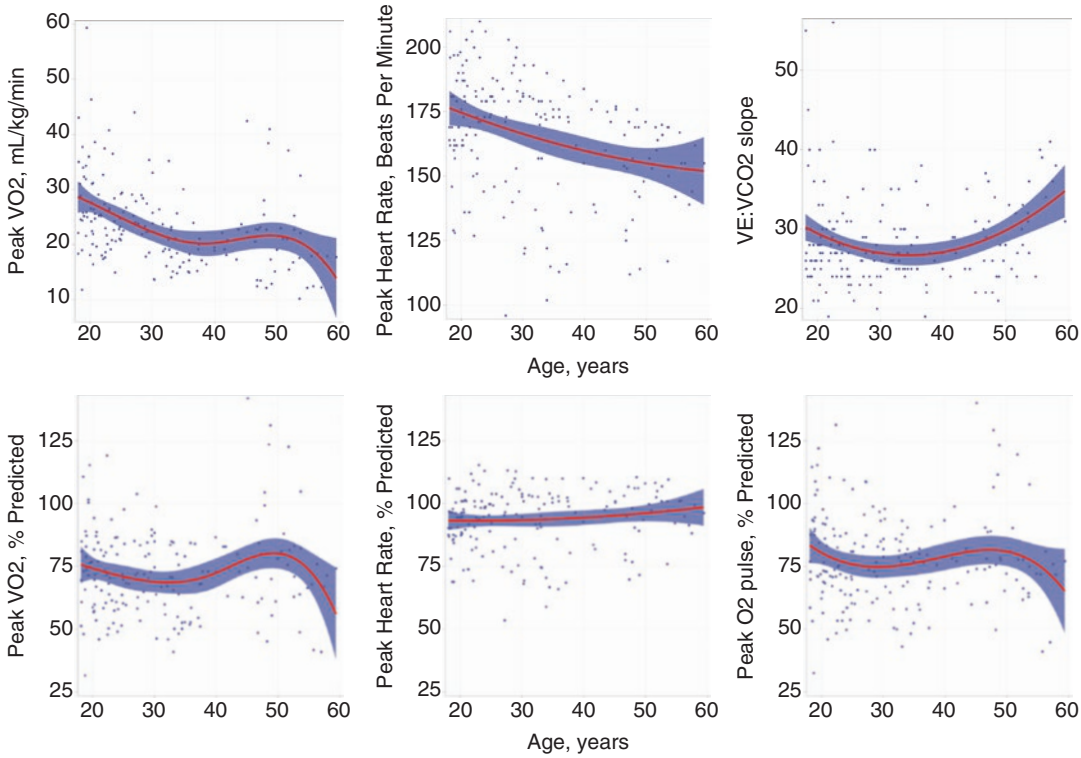


Fig. 20.1 Cardiopulmonary exercise test findings in patients with Ebstein anomaly who completed a maximal (respiratory exchange ratio >1.09) exercise test at Boston Children's Hospital between 2003 and 2017. Each point represents data for a single cardiopulmonary exercise test. The red line represents a restricted cubic spline fit to the data, with 95% confidence limits for the best fit line in semi-transparent blue. Only data for patients 10–60 years old with values between 20% and 150% predicted are presented. Note that the apparent increase in % predicted peak $\dot{V}_{O2}$ at ~50 years old is likely spurious, reflecting the relatively small sample size and the fact that three of the four observations >120% predicted were from tests on the same patient. Omitting those observations, the pattern is one of relative stability in peak $\dot{V}_{O2}$ as a percent predicted

mill. Description of exercise test results is provided in Table 20.1. On average, peak $\dot{V}_{O2}$ is slightly below normal. $\dot{V}_E/\dot{V}_{CO2}$ slope is normal for most (median 27). Notable hypoxemia at peak exercise with saturations <90% is observed in >5% of patients (fifth percentile nadir saturation 86%), presumably reflecting in many cases the presence of an atrial level communication with right-to-left shunt. Peak $\dot{V}_{O2}$ indexed to body mass declines steadily with age, though beyond adolescence there is little decline when $\dot{V}_{O2}$ is expressed as a percentage of predicted values. Chronotropic response tends to be normal while O_2 pulse is mildly impaired.

Prototypical Patient

The patient was an almost 20-year-old woman with severe Ebstein's anomaly. By physical examination and echocardiography she had severe tricuspid insufficiency. She also had marked dilation of the right atrium and the atrialized portion of her right ventricle (Ebstein severity grade was 4). Her estimated RV systolic pressure was normal and her LV function was also in the normal range. No atrial communication was detected.

Although she claimed to be asymptomatic, formal exercise testing (Fig. 20.2, Table 20.2)

Table 20.1 Boston Children's Hospital experience with Ebstein's anomaly patients who have had cardiopulmonary exercise tests 2003–2017

	n	Peak $\dot{V}_{O2}$ (% predicted)	Peak $\dot{V}_{O2}$ (mL/kg/min)	Peak HR (bpm)	Peak O_2 Pulse (% predicted)	$\dot{V}_E/\dot{V}_{CO2}$ slope	Resting O_2 saturation (%)	Peak O_2 saturation (%)
All	306	75±17	26±9	169±22	82±20	29±6	98±3	96±5
		49-64-74-87-102	15-20-25-31-43	129-155-171-184-200	51-70-80-93-119	22-25-27-31-40	93-98-98-99-100	86-97-98-98-99
≤ 18 years old	117	78±16	31±8	174±19	87±21	29±6	98±4	97±5
		52-67-80-90-100	20-25-30-37-45	141-162-175-190-203	56-74-89-98-123	22-25-27-31-43	91-98-98-99-100	83-97-98-98-99
19-30 years old	96	73±16	26±7	174±21	79±18	28±6	98±2	96±5
		49-61-72-84-102	18-22-25-29-41	134-162-179-187-203	53-67-76-90-110	21-24-27-30-40	93-98-98-99-100	83-97-98-98-99
> 30 years old	93	73±19	20±6	156±21	78±18	29±5	98±2	96±4
		46-61-71-83-105	12-17-19-23-35	115-142-160-173-184	50-67-77-86-112	22-25-28-33-38	94-97-98-98-100	89-95-97-98-99

Data are presented as mean ± SD with $_{5}$-$_{25}$-$_{50}$-$_{75}$-$_{95}^{th}$ percentiles in the row directly below

revealed moderately-severely depressed exercise function. Despite expending a good effort (reflected by a respiratory exchange ratio of 1.21 and heart rate of 176 bpm at peak exercise), her peak $\dot{V}_{O2}$ was only 59%predicted. A low peak work rate and low $\dot{V}_{O2}$ at the ventilatory anaerobic threshold (VAT) supported the peak $\dot{V}_{O2}$ findings. An inability to augment her forward stroke volume during exercise (reflected by her low O_2 pulse at peak exercise) appeared to be the primary factor responsible for her poor exercise function. Her peak heart rate was normal and her heart rate increased excessively for her level of $\dot{V}_{O2}$ during exercise, probably as a result of an autonomic response to the depressed stroke volume. Her gas exchange during exercise was normal and no arterial desaturation was detected (consistent with the absence of an atrial-level right-to-left shunt). Her breathing reserve was high, probably reflecting her inability to raise her metabolic rate normally secondary to her congenital heart disease. Compared to a CPET obtained 2 years earlier, her exercise function had declined significantly.

The difference between her perceived exercise function and the objective measurements obtained from the CPET probably related, at least in part, to the fact that she was born with a serious congenital heart defect and had never known what it is like to have a normal heart. A component of denial may also have accounted for the fact that she did not report and/or perceive the deterioration that had occurred over the past 2 years.

Following the CPET, she was referred for a tricuspid valvuloplasty (cone procedure). A subsequent CPET, performed ~2 years post-surgery, revealed that her peak $\dot{V}_{O2}$ had increased to 71%predicted and her O_2 pulse at peak exercise had increased 28% while achieving an identical peak heart rate (176 bpm). These observations suggested that the surgery had effectively enhanced her RV's ability to augment its forward stroke volume and increase cardiac output during exercise.

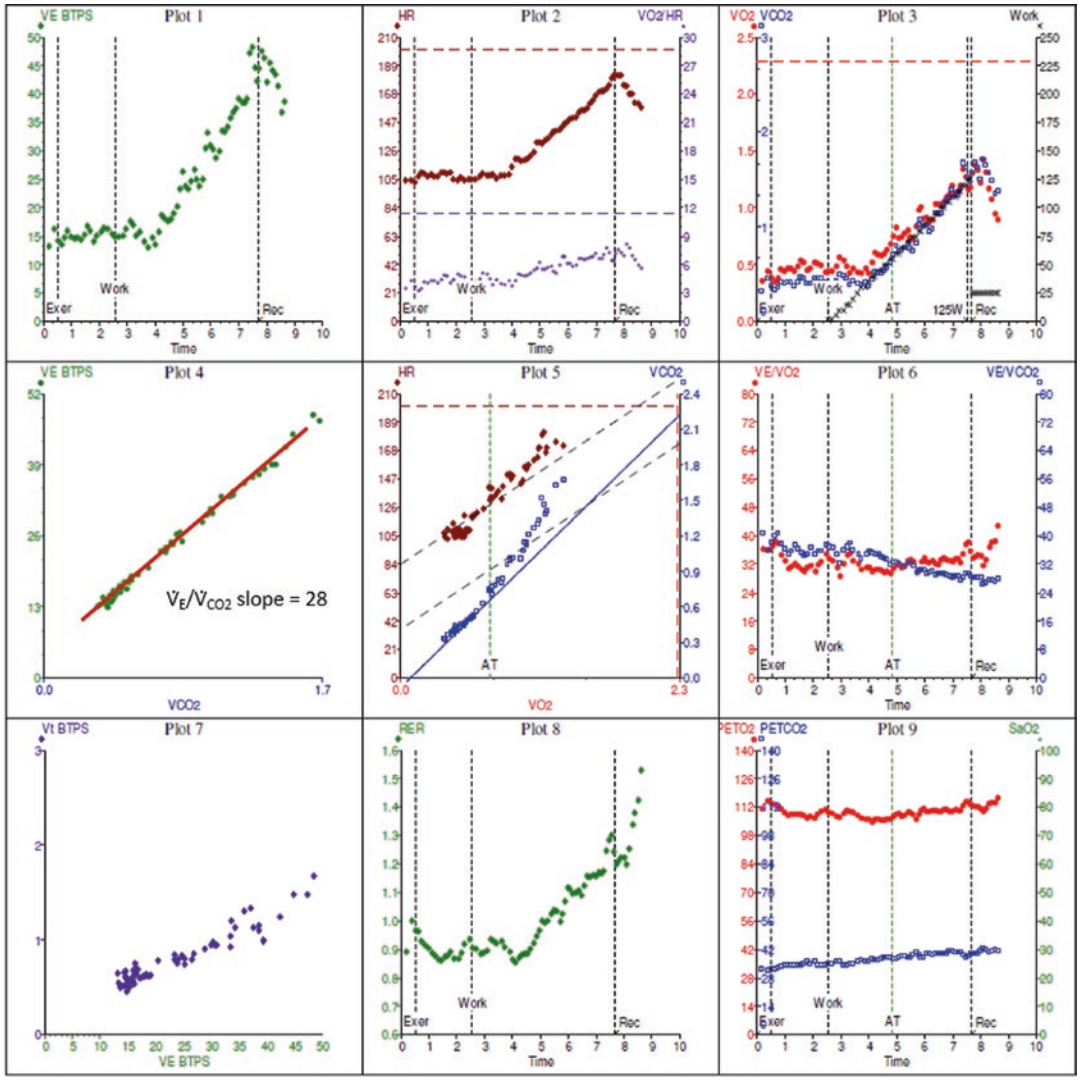


Fig. 20.2 9-panel graph of data from cardiopulmonary exercise test from prototypical patient. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, PETCO2 end-tidal pCO2, PETO2 end-tidal pO2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, $\dot{V}_{O2}$ oxygen consumption, $\dot{V}_{O2}$/HR oxygen pulse

Table 20.2 Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	18.2
Peak $\dot{V}_{O2}$ (%predicted)	59
Peak work rate (W)	120
Peak work rate (%predicted)	71
Peak RER	1.21
Peak O_2 pulse (%predicted)	62
Peak heart rate (bpm)	176
Peak heart rate (%predicted)	95
Heart rate increase	Excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	32
End-tidal pCO_2 at VAT (mm Hg)	38
End-tidal pCO_2 during exercise	Low-normal
$\dot{V}_E/\dot{V}_{CO2}$ slope	28
Forced vital capacity (%predicted)	105
FEV1 (%predicted)	86
FEF 25–75 (%predicted)	54
Breathing reserve (%)	58
Rhythm	Sinus rhythm throughout study
Blood pressure response	Normal
Oxygen saturation at rest (%)	99
Oxygen saturation at peak exercise (%)	99

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

References

1. Barbara DW, Edwards WD, Connolly HM, Dearani JA. Surgical pathology of 104 tricuspid valves (2000–2005) with classic right-sided Ebstein's malformation. Cardiovasc Pathol. 2008;17(3):166–71.
2. Arya P, Beroukhim R. Ebstein anomaly: assessment, management, and timing of intervention. Curr Treat Options Cardiovasc Med. 2014;16(10):338.
3. Cieplucha A, Trojnarska O, Kociemba A, Lanocha M, Barczynski M, Rozmiarek S, et al. Clinical aspects of myocardial fibrosis in adults with Ebstein's anomaly. Heart Vessel. 2018;33(9):1076–85.
4. Radojevic J, Inuzuka R, Alonso-Gonzalez R, Borgia F, Giannakoulas G, Prapa M, et al. Peak oxygen uptake correlates with disease severity and predicts outcome in adult patients with Ebstein's anomaly of the tricuspid valve. Int J Cardiol. 2013;163(3):305–8.
5. Daliento L, Angelini A, Ho SY, Frescura C, Turrini P, Baratella MC, et al. Angiographic and morphologic features of the left ventricle in Ebstein's malformation. Am J Cardiol. 1997;80(8):1051–9.
6. Muller J, Kuhn A, Tropschuh A, Hager A, Ewert P, Schreiber C, et al. Exercise performance in Ebstein's anomaly in the course of time – deterioration in native patients and preserved function after tricuspid valve surgery. Int J Cardiol. 2016;218:79–82.
7. Lupoglazoff JM, Denjoy I, Kabaker M, Benali K, Riescher B, Magnier S, et al. Cardiorespiratory exercise tolerance in asymptomatic children with Ebstein's anomaly. Pediatr Cardiol. 1999;20(3):189–94.
8. Chen SSM, Dimopoulos K, Sheehan FH, Gatzoulis MA, Kilner PJ. Physiologic determinants of exercise capacity in patients with different types of right-sided regurgitant lesions: Ebstein's malformation with tricuspid regurgitation and repaired tetralogy of fallot with pulmonary regurgitation. Int J Cardiol. 2016;205:1–5.
9. Kipps AK, Graham DA, Lewis E, Marx GR, Banka P, Rhodes J. Natural history of exercise function in patients with Ebstein anomaly: a serial study. Am Heart J. 2012;163(3):486–91.
10. Trojnarska O, Szyszka A, Gwizdala A, Siniawski A, Oko-Sarnowska Z, Chmara E, et al. Adults with Ebstein's anomaly – cardiopulmonary exercise testing and bnp levels exercise capacity and bnp in adults with Ebstein's anomaly. Int J Cardiol. 2006;111(1):92–7.
11. Gentles TL, Calder AL, Clarkson PM, Neutze JM. Predictors of long-term survival with Ebstein's anomaly of the tricuspid valve. Am J Cardiol. 1992;69(4):377–81.
12. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Developed in collaboration with the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52(23):e143–263.
13. Luu Q, Choudhary P, Jackson D, Canniffe C, McGuire M, Chard R, et al. Ebstein's anomaly in those surviving to adult life – a single centre experience. Heart Lung Circ. 2015;24(10):996–1001.

Pulmonary Vascular Disease

21

Jonathan Rhodes and Alexander R. Opotowsky

Basic Anatomy and Pathophysiology

The classic histopathology of pulmonary vascular obstructive disease is characterized by intimal thickening/proliferation, medial hypertrophy, and ultimately "plexiform lesions," fibrosis, and scarring of the walls of the precapillary pulmonary arteries and arterioles. These histologic abnormalities result in partial or complete vessel obstruction and a consequent reduction of the number and total cross-sectional area of these pulmonary blood vessels. The endothelial function and vasodilatory capacity of the remaining, patent blood vessels are also impaired. These structural and functional abnormalities appear to represent a final common pathway of multiple conditions. Conditions that are associated with the development of pulmonary vascular disease include idiopathic pulmonary arterial hypertension (PAH), familial PAH, or PAH due to de novo genetic defects (e.g., bone morphogenic protein receptor type 2 mutations), or PAH associated with toxin exposure, inflammation, congenital heart disease, or left-sided heart disease. Other etiologies relevant to pediatric patients are conditions associated with hypoplasia of the lungs and/or pulmonary vascular bed secondary to birth defects (e.g., in patients with congenital diaphragmatic hernias), pediatric chronic lung diseases (e.g., bronchopulmonary dysplasia) and developmental lung diseases (e.g., alveolar capillary dysplasia, hereditary hemorrhagic telangiectasia, and pulmonary veno-occlusive disease). It seems that the shear stress related to pulmonary hypertension can, by itself, cause ongoing damage/injury to the pulmonary vascular bed resulting in the histopathology described above. This damage elevates pulmonary vascular resistance and pulmonary artery (PA) pressures, which then causes more damage, and so on. Consequently, without effective treatment the disease tends to be progressive and relentless [1–5].

Certainly PAH, defined simply as elevated pulmonary artery pressure, can be present in the absence of the severe histologic changes described

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

A. R. Opotowsky
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Exercise Physiology Laboratory, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: alexander.opotowsky@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_21

previously. For instance, it may result from high pulmonary blood flow ± pulmonary vasoconstriction (as in the case of an infant with a large ventricular septal defect or patent ductus arteriosus), or because of elevated pulmonary venous pressure (which is also often associated with disproportionate pulmonary vasoconstriction), as can be seen with various forms of left-sided heart disease. These alternative causes of elevated pulmonary artery pressure can, however, lead to progressive and potentially irreversible pulmonary vascular damage over time. Determining the contributions of various factors responsible for elevated pulmonary artery pressure is often key to determining appropriate therapy [6].

Hemodynamics

The abnormalities of the pulmonary vascular bed previously described result in elevated pulmonary vascular resistance (PVR) and PA pressure, both at rest and during exercise. Normally, PVR declines with exercise; loss of the capacity for this normal decline is presumably an early victim of the decrease in pulmonary vascular bed cross-sectional area and/or the vasodilatory capacity of the pulmonary arteriolar resistance vessels. Accurate measurement of PVR during exercise requires invasive testing, however. Initially, the component of the elevated pressure and resistance that is due to medial hypertrophy and increased vascular tone may be partially reversible and responsive to pharmacologic pulmonary vasodilation. Idiopathic PAH tends to be more likely to respond to acute vasodilation challenges, though only a minority demonstrate a robust response. As the disease progresses and the fibrosis/scarring of the pulmonary vascular bed becomes more extensive, the response to vasodilator therapy tends to become more attenuated [1, 7].

PAH imposes increased afterload upon the right ventricle (RV). Initially the RV responds by adaptive myocardial hypertrophy. However, as the disease progresses and the pulmonary vascular resistance relentlessly increases, progressive RV dilation/dysfunction develops. RV dysfunction may be due, in part, to RV ischemia secondary to the increased myocardial oxygen demand that results from the increased workload imposed upon the RV by the elevated pulmonary vascular resistance [7, 8]. These phenomena cause the right atrial and RV diastolic pressures to rise as the RV moves up its (often depressed) Starling curve in order to accommodate the excessive workload. The degree of right atrial pressure elevation is strongly associated with prognosis, as it reflects the RV's failure/decompensation in the face of the excessive afterload imposed upon it by the pulmonary hypertension [9, 10]. RV dilation and elevated right-sided pressures can also result in tricuspid and/or pulmonary regurgitation. These factors combine to impair the RV's ability to maintain adequate stroke volume and cardiac output during exercise [1, 7, 11].

In patients with a patent foramen ovale or other atrial communication, right-to-left shunting can develop, especially during exercise as the RV moves up its Starling curve and RV diastolic and right atrial pressures rise to equal or exceed the left atrial pressure. This can also occur in the context of abnormal streaming due to tricuspid regurgitation or other causes. This phenomenon causes systemic arterial desaturation [1, 11]. It will also cause an increase in the $\dot{V}_E/\dot{V}_{CO2}$ ratio and a decrease in the end-tidal pCO_2 (Fig. 21.1, and see Chap. 12) [11].

Pulmonary venous desaturation can also be present in patients with pulmonary vascular disease. In some cases, this anomaly may be a consequence of impaired oxygen diffusion across the alveolar-capillary membrane [12, 13] and/or ventilation/perfusion (*V/Q*) mismatch [14, 15]. This phenomenon may also result from the inordinately rapid red cell transit time that is associated with this condition, especially during exercise. Occlusion/obstruction of the small pulmonary arteries and arterioles forces red blood cells to travel through a restrictive pulmonary vascular bed. Because pulmonary blood flow (i.e., volume per time interval) is equal to the cross-sectional area of the pulmonary vascular bed multiplied by the velocity of the blood flowing through the vascular bed, the restrictive (i.e., diminished cross-sectional area) pulmonary vascular bed causes the velocity of the red blood cells within the pulmonary vascular bed to be increased. The red blood

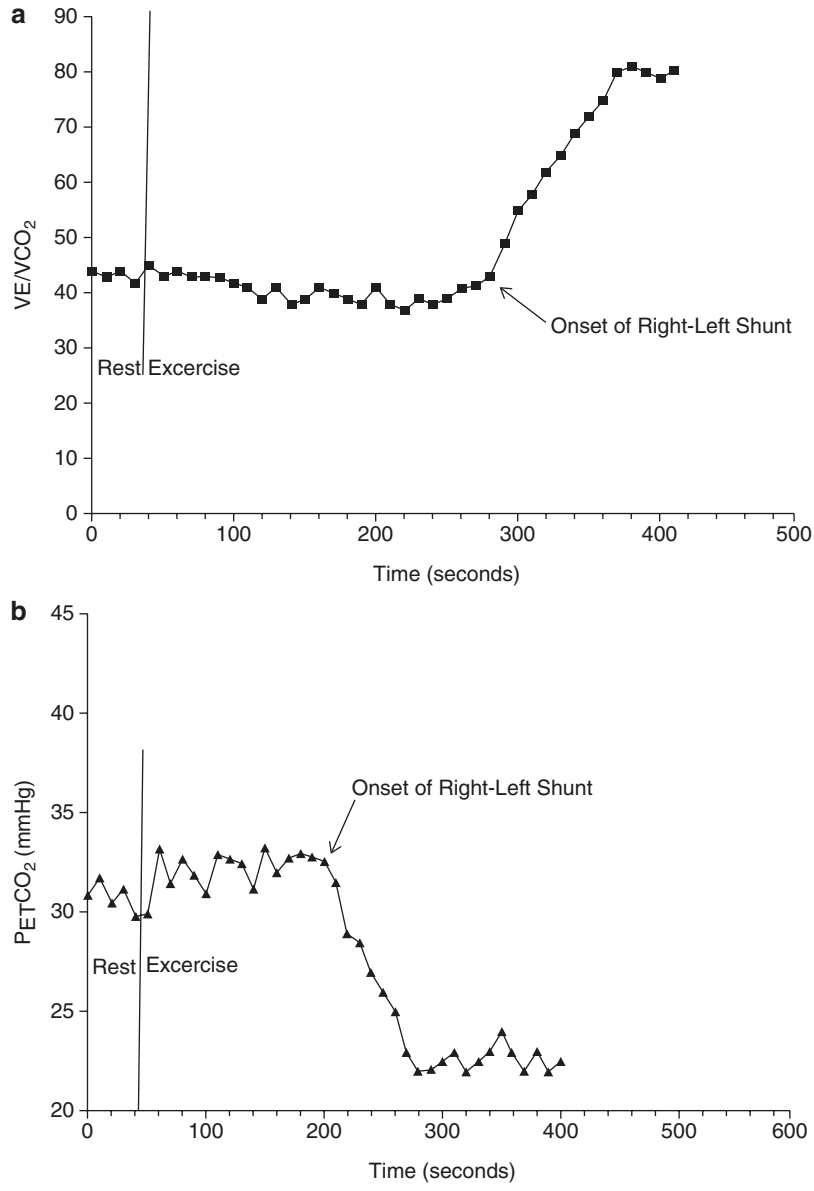


Fig. 21.1 Example of a $\dot{V}_E/\dot{V}_{CO2}$ ratio and $P_{ET}CO_2$ response in a patient with primary pulmonary hypertension who developed a right-to-left shunt during exercise testing. (**a**) $\dot{V}_E/\dot{V}_{CO2}$ ratio response. (**b**) $P_{ET}CO_2$ response. (Arena et al. [11])

cells therefore pass quickly through the alveolar capillaries and the time available to participate in gas exchange will be abbreviated. Consequently, the pO_2 within the red blood cell may not have equilibrated with the pO_2 within the alveolus by the time it exits the alveolar capillaries, and the hemoglobin will not be fully saturated [11, 16]. (Because CO_2 diffuses across the alveolar-capillary membrane much more rapidly than does O_2, the pCO_2 of the blood and alveolus usually are in equilibrium by the time the blood leaves the alveolar capillaries, even in the presence of severe pulmonary vascular disease.)

Exercise Function

The peak $\dot{V}_{O2}$ of patients with PAH is almost always depressed, primarily on account of an inability to increase the oxygen pulse normally

with exercise [11, 17, 18]. This reflects the right ventricle's inability to increase the forward stroke volume. The ventilatory anaerobic threshold (VAT) is also depressed. This phenomenon is once again due to the fact that the low cardiac output during exercise and the arterial desaturation (if present) compromise oxygen delivery to the muscles and cause an earlier-than-normal reliance upon anaerobic metabolism [11]. This physiology also results in a depressed $\dot{V}_{O2}$/work rate relationship [17, 18].

Ventilatory Function

On a microscopic level, some degree of *V/Q* mismatch secondary to the pulmonary vascular obstruction inherent to pulmonary vascular disease would be expected to be virtually universal. On a macroscopic level, this conjecture has been confirmed by studies of *V/Q* mismatch using the multiple inert gas elimination technique [15]. During exercise, the *V/Q* mismatch almost always results in inefficient gas exchange and excessive ventilation during exercise, manifested by an elevated $\dot{V}_E/\dot{V}_{CO2}$ slope (and the $\dot{V}_E/\dot{V}_{CO2}$ ratio) [7, 11, 17, 19, 20]. End-tidal pCO_2 during exercise also tends to be low in patients with pulmonary vascular disease, as areas of the lung with decreased or absent perfusion essentially act as dead space [7, 11, 17]. The pCO_2 in the alveoli from these areas will be close to zero, will dilute out CO_2 in the expired air from the better-perfused alveoli and thereby lower the end-tidal pCO_2. Right-to-left intracardiac shunting, if present, will also tend to elevate the $\dot{V}_E/\dot{V}_{CO2}$ slope and lower the end-tidal pCO_2 [11] (see Chap. 12).

Clinical Implications

Studies have found that peak $\dot{V}_{O2}$ is a powerful predictor of adverse prognosis in patients with PAH, probably because it reflects the ability of the right ventricle to accommodate the hemodynamic burdens imposed by the disease [11, 21]. As the disease progresses, the ability of the RV to accommodate these burdens (especially during physical activity) becomes more and more impaired, and the peak $\dot{V}_{O2}$ declines. Consequently, peak $\dot{V}_{O2}$ has been found to be an excellent predictor of mortality in patients with pulmonary hypertension [20–22]. For instance, in a study of 70 patients with PAH, Wensel et al. found that the peak $\dot{V}_{O2}$ and the peak-exercise systolic blood pressure (BP) were the strongest predictors of mortality. Among patients with a peak $\dot{V}_{O2}$ < 10.4 ml/kg/min and a peak systolic BP <120 mm Hg, 1-year survival was only 23%. In contrast, the 1-year survival of patients with peak $\dot{V}_{O2} \geq 10.4$ ml/kg/min and peak systolic BP ≥120 mm Hg was 97%. Similarly, in a study of 40 pediatric patients with pulmonary hypertension (mean age 13.4 ± 7.5 years), Yetman et al. reported that peak $\dot{V}_{O2}$ was significantly lower among patients with adverse clinical outcomes [20]. The peak $\dot{V}_{O2}$ has also been found to correlate strongly with many catheterization-derived hemodynamic variables including pulmonary vascular resistance, pulmonary to systemic vascular resistance ratio, pulmonary artery pressures, pulmonary capillary wedge pressure, and mean right atrial pressure [19, 21, 23]. Interestingly, peak $\dot{V}_{O2}$ correlates most closely with mean right atrial pressure, which, as noted earlier, is the hemodynamic variable that is most closely associated with prognosis [21, 23]. Patients with a peak $\dot{V}_{O2}$ > 75% of predicted are also more likely to have a positive response to acute pulmonary vasodilator testing [23]. This suggests that this subset of patients may be able to benefit from dynamic vasodilation during exercise, permitting a more robust cardiac output response.

The *V/Q* mismatch associated with pulmonary vascular disease also worsens as the disease progresses. This phenomenon is reflected by progressive elevation of the $\dot{V}_E/\dot{V}_{CO2}$ slope. Consequently, the $\dot{V}_E/\dot{V}_{CO2}$ slope has been found to be a good index of disease severity and to carry powerful prognostic implications (Fig. 21.2) [11, 21].

Cardiopulmonary exercise testing (CPET) can also serve as a valuable tool for the objective and quantitative assessment of response to PAH therapeutic interventions [24–30]. Yet, it must be acknowledged that interventional studies have

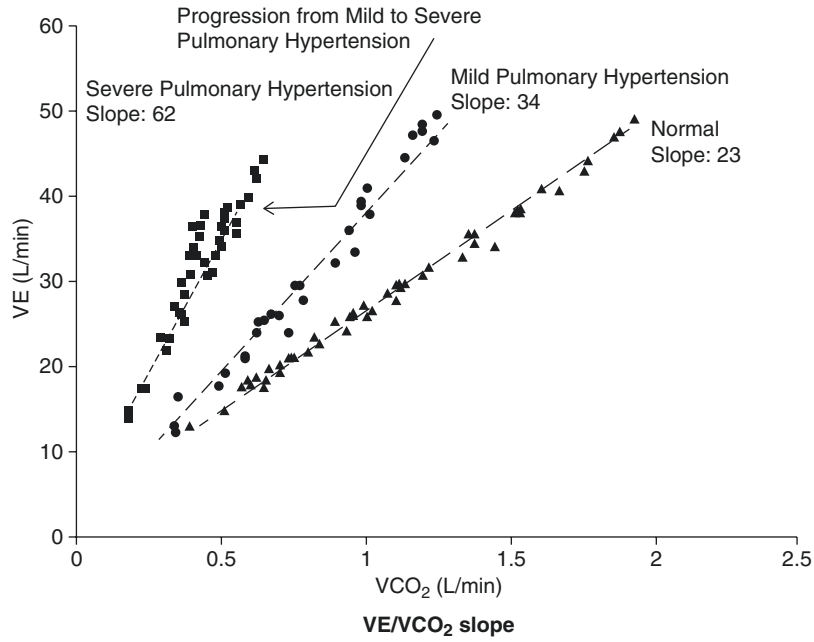


Fig. 21.2 Example of ventilatory expired gas responses in an apparently healthy individual and patients with pulmonary hypertension during a progressive maximal exercise test. (Reprinted with permission from Arena et al. [11])

more often relied upon the 6 minute walk test (6MWT) as a surrogate clinical end point. The distance walked on a baseline 6MWT correlates with survival in patients with PAH [31–34]. Changes in 6MWT distance have also sometimes been found to correlate with survival and/or changes in invasive hemodynamic measurements in response to treatment [29, 34–36]. The correlation between 6MWT distance and peak $\dot{V}_{O2}$ is generally but not uniformly good [29, 30]. The advantages of the 6MWT include its simplicity, low cost, greater resemblance to day-to-day submaximal physical activities, and evidence base in pulmonary hypertension and other cardiovascular disorders (e.g., congestive heart failure). The disadvantages of this test include the fact that the distance walked may be influenced by many factors that may affect a patient's mobility but are not directly related to the underlying pulmonary vascular disease, e.g., the patient's weight, stride length, walking and turning skills, cooperation, motivation, experience, and neurologic and musculoskeletal issues. Unlike with CPET where respiratory exchange ratio (RER) (and peak heart rate) provides a strong indication of maximal physiologic effort, there is no such indicator or equivalent effort on the 6MWT. Consequently, there is a small "signal to noise ratio" for 6MWT data. This issue may be mitigated, at least in part, by the large sample sizes employed by some research studies. For an individual patient, however, relying on 6MWT data to reflect a response to therapy is often dubious. Furthermore, in all but the most limited patients (including most children/adolescents), the 6MWT is a submaximal test, and there is a significant "ceiling effect"; i.e., it is hard to improve upon a high 6MWT distance [37]. Indeed, the reliability and meaning of the 6MWT for patients who can walk more than ~400 meters has been questioned [38]. Hence, although it correlates fairly well with peak $\dot{V}_{O2}$ in highly symptomatic patients, the utility and validity of the 6MWT in patients with "only" mild or moderate impairments is questionable [39]. The advantages of CPET in this context—i.e., the physiologic insights it provides, its internal checks, superior reproducibility (when conducted in an experienced laboratory), biologic plausibility, and prognostic power—have been recognized [40, 41].

In some patients with normal or borderline-elevated PA pressures at rest, an excessive rise in PA pressures may be detected with stress echocardiography [42] or invasive CPETs [43–45].

This abnormal response has been predictive of the development of resting pulmonary hypertension in the future, at least in some patient populations [46]. In these patients an elevated $\dot{V}_E/\dot{V}_{CO2}$ slope is also likely to be encountered [43]. There are numerous reasons for elevated right ventricular systolic pressure with exercise, however, including increased pulmonary venous pressure or development of a dynamic flow-related right ventricular outflow tract gradient [44, 47].

Despite concern to the contrary, exercise testing appears to carry low-risk in patients with pulmonary hypertension. In a meta-analysis that reviewed 23 studies of CPET in patients with pulmonary hypertension, Arena et al. were unable to find a single case of a reported adverse event. It must be noted, however, that none of the studies was very large, and 11 of them include fewer than 20 pulmonary hypertension patients. Moreover, many centers consider exercise testing to be contraindicated in PAH associated with syncope, acute right ventricular failure, or arrhythmia. It is therefore likely that some of the highest risk patients were excluded from some of the studies. It should also be noted, however, that several small studies have recently concluded that well-designed, moderate exercise training programs can safely improve the exercise capacity and quality of life of patients with PAH who are stable on PAH-specific pharmacologic therapy [7, 48–54].

Prototypical Patient

The patient was a 15-year-old adolescent female who was diagnosed with idiopathic pulmonary hypertension. She was treated with trepostinil, tadalafil, and ambrisentan. At a catheterization 4 months prior to the exercise test, her PA pressures were elevated to systemic levels, and her right atrial pressure was elevated to 14 mm Hg. By history, her exercise tolerance was quite poor. She was referred to the exercise laboratory to better characterize her current functional and cardiopulmonary status.

Table 21.1 Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	12.6
Peak $\dot{V}_{O2}$ (%predicted)	37
Peak work rate (W)	52
Peak work rate (%predicted)	39
Peak RER	1.14
Peak O2 pulse (%predicted)	49
Peak heart rate (bpm)	144
Peak heart rate (%predicted)	76
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	28
Arterial oxygen saturation	Normal
Breathing reserve (%)	57
$\dot{V}_E/\dot{V}_{CO2}$ slope	51
End-tidal pCO_2 at VAT (mm Hg)	23
End-tidal pCO_2 during exercise	Very low
Forced vital capacity (%predicted)	74
FEV1 (%predicted)	75
FEF 25–75 (%predicted)	76
Breathing reserve (%)	57
Blood pressure response	Normal

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold *FEV1* volume exhaled during the first second of forced expiration *FEF* Flow rate between 25 and 75% of a forced expiration

The CPET (Table 21.1 and Fig. 21.3) was performed on a cycle ergometer using a 10 W/min ramp. The exercise test was terminated due to chest pain (5/10). The RER at peak exercise was 1.14, indicating that the patient expended an adequate effort. Her peak work rate, peak $\dot{V}_{O2}$, peak O_2 pulse and $\dot{V}_{O2}$ at the VAT were quite low. Moreover, the O_2 pulse did not increase significantly during exercise. The patient's heart rate rose excessively rapidly during exercise and her peak heart rate was only mildly depressed. Her $\dot{V}_E/\dot{V}_{CO2}$ slope was extremely high, and her end-tidal pCO_2 during exercise was quite low. Her arterial oxygen saturation remained normal throughout the study. Her baseline electrocardiogram (EKG) revealed right ventricular hypertrophy with strain. No significant additional STT changes developed during exercise or recovery. No ectopy was detected during exercise. Rare premature ventricular contractions were noted during recovery. Only mild abnormalities were present on baseline spirometry and the breathing

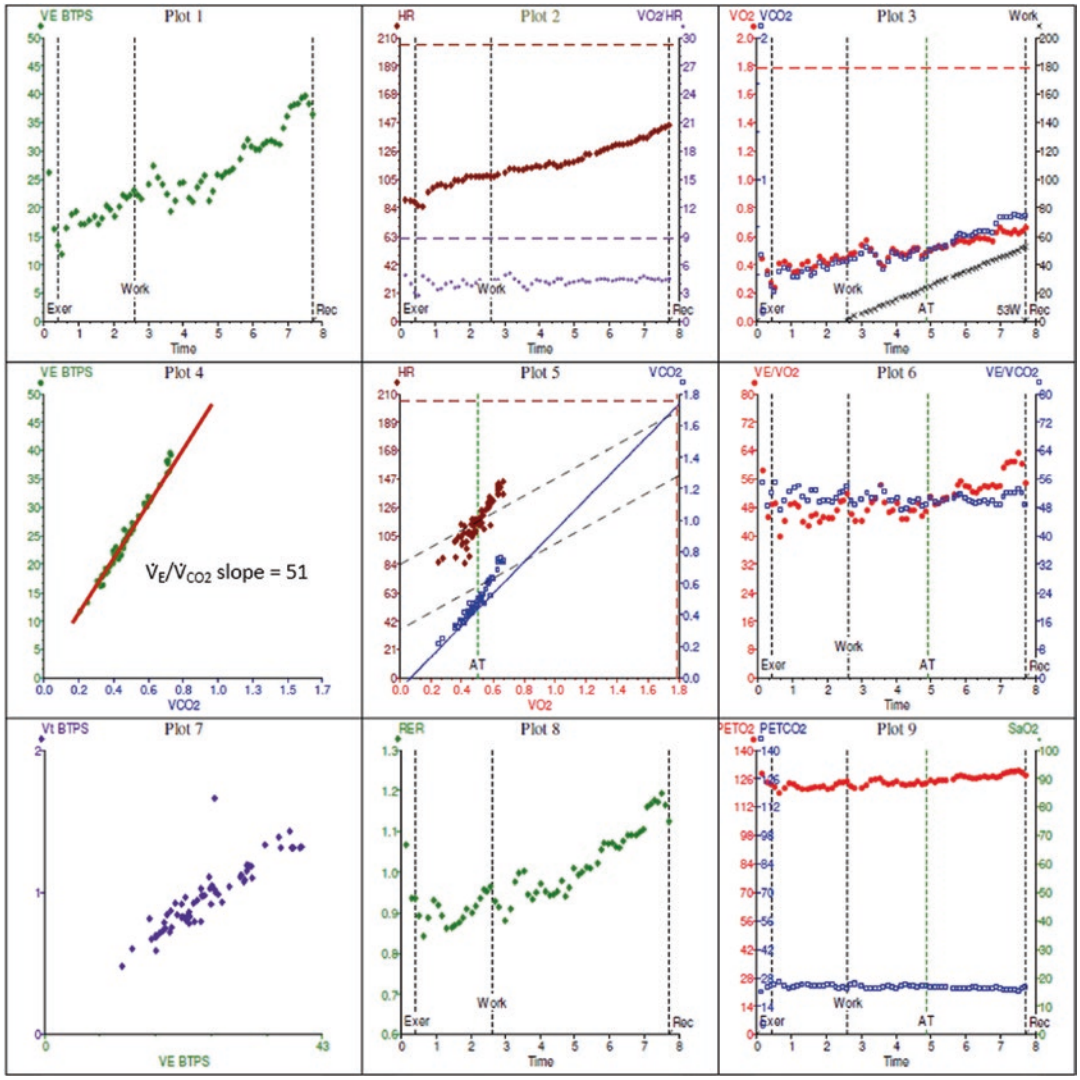


Fig. 21.3 Nine-panel graph from cardiopulmonary exercise test on prototypical patient with pulmonary vascular disease. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, PETCO2 end-tidal pCO2, PETO2 end-tidal pO2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, V_E minute ventilation, $\dot{V}_{O2}$ oxygen consumption, V_{O2}/HR oxygen pulse

reserve at peak exercise was high, indicating that exercise was not terminated due to respiratory factors.

The low oxygen pulse at peak exercise and the failure of the O_2 pulse to increase significantly during exercise probably reflect the fact that the high afterload imposed upon the RV by the patient's pulmonary vascular disease impaired its ability to augment its stroke volume during exercise. The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 were probably the consequences of the V/Q mismatch that almost always accompanies pulmonary vascular disease. The normal arterial oxygen saturation suggests that right-to-left intracardiac shunting was not present (no septal defects or other communications were detected by echocardiography or cardiac catheterization) and that gas exchange across the alveolar-capillary membrane

was not impaired. The exercise-induced chest pain may have been due to RV ischemia secondary to the inordinately high RV myocardial oxygen demand that develops as the RV is forced to accommodate the hemodynamic demands of exercise in the setting of markedly elevated pulmonary artery pressures and resistance.

References

1. Haworth SG. Primary pulmonary hypertension in childhood. Arch Dis Child. 1998;79(5):452–5.
2. Hansmann G. Pulmonary hypertension in infants, children, and young adults. J Am Coll Cardiol. 2017;69(20):2551–69.
3. Ivy D. Pulmonary hypertension in children. Cardiol Clin. 2016;34(3):451–72.
4. Ivy DD, Abman SH, Barst RJ, Berger RM, Bonnet D, Fleming TR, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D117–26.
5. Hopper RK, Abman SH, Ivy DD. Persistent challenges in pediatric pulmonary hypertension. Chest. 2016;150(1):226–36.
6. Opotowsky AR. Clinical evaluation and management of pulmonary hypertension in the adult with congenital heart disease. Circulation. 2015;131(2):200–10.
7. Fowler RM, Gain KR, Gabbay E. Exercise intolerance in pulmonary arterial hypertension. Pulm Med. 2012;2012:359204.
8. Vonk Noordegraaf A, Galie N. The role of the right ventricle in pulmonary arterial hypertension. Eur Respir Rev. 2011;20(122):243–53.
9. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115(5):343–9.
10. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med. 1987;107(2):216–23.
11. Arena R, Lavie CJ, Milani RV, Myers J, Guazzi M. Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. J Heart Lung Transplant. 2010;29:159–73.
12. Steenhuis LH, Groen HJ, Koeter GH, van der Mark TW. Diffusion capacity and haemodynamics in primary and chronic thromboembolic pulmonary hypertension. Eur Respir J. 2000;16(2):276–81.
13. Oppenheimer BW, Berger KI, Hadjiangelis NP, Norman RG, Rapoport DM, Goldring RM. Membrane diffusion in diseases of the pulmonary vasculature. Respir Med. 2006;100(7):1247–53.
14. Melot C, Naeije R, Mols P, Vandenbossche JL, Denolin H. Effects of nifedipine on ventilation/perfusion matching in primary pulmonary hypertension. Chest. 1983;83(2):203–7.
15. Bratel T, Lagerstrand L, Brodin LA, Nowak J, Randmaa I. Ventilation-perfusion relationships in pulmonary arterial hypertension: effect of intravenous and inhaled prostacyclin treatment. Respir Physiol Neurobiol. 2007;158(1):59–69.
16. Presson RG Jr, Graham JA, Hanger CC, Godbey PS, Gebb SA, Sidner RA, et al. Distribution of pulmonary capillary red blood cell transit times. J Appl Physiol (1985). 1995;79(2):382–8.
17. Riley MS, Porszasz J, Engelen MP, Brundage BH, Wasserman K. Gas exchange responses to continuous incremental cycle ergometry exercise in primary pulmonary hypertension in humans. Eur J Appl Physiol. 2000;83(1):63–70.
18. D'Alonzo GE, Gianotti LA, Pohil RL, Reagle RR, DuRee SL, Fuentes F, et al. Comparison of progressive exercise performance of normal subjects and patients with primary pulmonary hypertension. Chest. 1987;92(1):57–62.
19. Rausch CM, Taylor AL, Ross H, Sillau S, Ivy DD. Ventilatory efficiency slope correlates with functional capacity, outcomes, and disease severity in pediatric patients with pulmonary hypertension. Int J Cardiol. 2013;169(6):445–8.
20. Yetman AT, Taylor AL, Doran A, Ivy DD. Utility of cardiopulmonary stress testing in assessing disease severity in children with pulmonary arterial hypertension. Am J Cardiol. 2005;95(5):697–9.
21. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken G, Kleber FX, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation. 2002;106(3):319–24.
22. Groepenhoff H, Vonk-Noordegraaf A, Boonstra A, Spreeuwenberg MD, Postmus PE, Bogaard HJ. Exercise testing to estimate survival in pulmonary hypertension. Med Sci Sports Exerc. 2008;40(10):1725–32.
23. Rhodes J, Barst RJ, Garofano RP, Thoele DG, Gersony WM. Hemodynamic correlates of exercise function in patients with primary pulmonary hypertension. J Am Coll Cardiol. 1991;18(7):1738–44.
24. Wax D, Garofano R, Barst RJ. Effects of long-term infusion of prostacyclin on exercise performance in patients with primary pulmonary hypertension. Chest. 1999;116(4):914–20.
25. Wensel R, Opitz CF, Ewert R, Bruch L, Kleber FX. Effects of iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. Circulation. 2000;101(20):2388–92.
26. Riley MS, Porszasz J, Engelen MP, Shapiro SM, Brundage BH, Wasserman K. Responses to constant work rate bicycle ergometry exercise in primary pulmonary hypertension: the effect of inhaled nitric oxide. J Am Coll Cardiol. 2000;36(2):547–56.
27. Nagaya N, Shimizu Y, Satoh T, Oya H, Uematsu M, Kyotani S, et al. Oral beraprost sodium improves

exercise capacity and ventilatory efficiency in patients with primary or thromboembolic pulmonary hypertension. Heart. 2002;87(4):340–5.
28. Barst RJ, McGoon M, McLaughlin V, Tapson V, Rich S, Rubin L, et al. Beraprost therapy for pulmonary arterial hypertension. J Am Coll Cardiol. 2003;41(12):2119–25.
29. Barst RJ, Langleben D, Frost A, Horn EM, Oudiz R, Shapiro S, et al. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med. 2004;169(4):441–7.
30. Oudiz RJ, Barst RJ, Hansen JE, Sun XG, Garofano R, Wu X, et al. Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension. Am J Cardiol. 2006;97(1):123–6.
31. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2000;161(2 Pt 1):487–92.
32. Williams MH, Das C, Handler CE, Akram MR, Davar J, Denton CP, et al. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. Heart. 2006;92(7):926–32.
33. Boucly A, Weatherald J, Humbert M, Sitbon O. Risk assessment in pulmonary arterial hypertension. Eur Respir J. 2018;51(3):407–15.
34. Provencher S, Sitbon O, Humbert M, Cabrol S, Jais X, Simonneau G. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. Eur Heart J. 2006;27(5):589–95.
35. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996;334(5):296–301.
36. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353(20):2148–57.
37. Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-a receptor antagonist sitaxsentan. J Am Coll Cardiol. 2006;47(10):2049–56.
38. Gratz A, Hess J, Hager A. Peak oxygen uptake and exercise capacity: a reliable predictor of quality of life? Reply. Eur Heart J. 2009;30:1674–5.
39. Olsson LG, Swedberg K, Clark AL, Witte KK, Cleland JG. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. Eur Heart J. 2005;26(8):778–93.
40. Hassoun PM, Nikkho S, Rosenzweig EB, Moreschi G, Lawrence J, Teeter J, et al. Updating clinical endpoint definitions. Pulm Circ. 2013;3(1):206–16.
41. Snow JL, Kawut SM. Surrogate end points in pulmonary arterial hypertension: assessing the response to therapy. Clin Chest Med. 2007;28(1):75–89, viii.
42. D'Alto M, Bossone E, Opotowsky AR, Ghio S, Rudski LG, Naeije R. Strengths and weaknesses of echocardiography for the diagnosis of pulmonary hypertension. Int J Cardiol. 2018;263:177–83.
43. Oliveira RKF, Faria-Urbina M, Maron BA, Santos M, Waxman AB, Systrom DM. Functional impact of exercise pulmonary hypertension in patients with borderline resting pulmonary arterial pressure. Pulm Circ. 2017;7(3):654–65.
44. van Riel AC, Opotowsky AR, Santos M, Rivero JM, Dhimitri A, Mulder BJ, et al. Accuracy of echocardiography to estimate pulmonary artery pressures with exercise: a simultaneous invasive-noninvasive comparison. Circ Cardiovasc Imaging. 2017;10(4):407–15
45. Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM. Exercise-induced pulmonary arterial hypertension. Circulation. 2008;118(21):2183–9.
46. Codullo V, Caporali R, Cuomo G, Ghio S, D'Alto M, Fusetti C, et al. Stress doppler echocardiography in systemic sclerosis: evidence for a role in the prediction of pulmonary hypertension. Arthritis Rheum. 2013;65(9):2403–11.
47. Wright SP, Opotowsky AR, Buchan TA, Esfandiari S, Granton JT, Goodman JM, et al. Flow-related right ventricular—pulmonary arterial pressure gradients during exercise. Cardiovasc Res. 2018;222–9.
48. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation. 2006;114(14):1482–9.
49. de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJ, et al. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. Eur Respir J. 2009;34(3):669–75.
50. Mainguy V, Maltais F, Saey D, Gagnon P, Martel S, Simon M, et al. Effects of a rehabilitation program on skeletal muscle function in idiopathic pulmonary arterial hypertension. J Cardiopulm Rehabil Prev. 2010;30(5):319–23.
51. Grunig E, Ehlken N, Ghofrani A, Staehler G, Meyer FJ, Juenger J, et al. Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. Respiration. 2011;81(5):394–401.
52. Chan L, Chin LMK, Kennedy M, Woolstenhulme JG, Nathan SD, Weinstein AA, et al. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. Chest. 2013;143(2):333–43.
53. Fox BD, Kassirer M, Weiss I, Raviv Y, Peled N, Shitrit D, et al. Ambulatory rehabilitation improves exercise capacity in patients with pulmonary hypertension. J Card Fail. 2011;17(3):196–200.
54. Arena R, Lavie CJ, Borghi-Silva A, Daugherty J, Bond S, Phillips SA, et al. Exercise training in group 2 pulmonary hypertension: which intensity and what modality. Prog Cardiovasc Dis. 2016;59(1):87–94.

22 Exercise Testing in Pediatric Dilated Cardiomyopathy

Irene D. Lytrivi and T. P. Singh

Dilated cardiomyopathy is the most common cardiomyopathy in children with an incidence of 0.56/100,000 per year [1]. The diagnosis is established by cardiac imaging, which demonstrates a dilated left ventricle (LV) with reduced systolic function. LV diastolic dysfunction and right ventricular systolic dysfunction may also develop [2]. Outcome varies with the underlying cause (such as infections, toxins, inborn errors of metabolism, or genetic mutations), the degree of LV systolic dysfunction, and the severity of symptoms [3]. In a large cohort of children seen at tertiary care centers in North America, the overall 1- and 5-year rates of death or transplantation after initial diagnosis were 31% and 46%, respectively [1].

I. D. Lytrivi (✉)
Department of Pediatrics, Columbia University Medical College, New York, NY, USA

Program for Pediatric Cardiomyopathy, Heart Failure and Transplantation, Division of Pediatric Cardiology, Columbia Presbyterian Hospital, New York, NY, USA
e-mail: Idl2108@cumc.columbia.edu

T. P. Singh
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Heart Failure/Transplant Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: TP.singh@cardio.chboston.org

Pathophysiology

The initial myocardial injury and resulting decrease in cardiac output lead to the activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. These compensatory responses help in maintaining cardiac output and blood pressure. However, prolonged myocardial exposure to angiotensin and sympathetic hormones results in changes at the molecular, cellular (apoptosis, hypertrophy, reduced beta-receptor density), interstitial (fibrosis) and morphologic (progressive LV dilation and dysfunction) levels collectively described as "LV remodeling." Remodeling is potentially beneficial in the short term but becomes maladaptive if sustained [4].

With progressive LV dysfunction, the patient's ability to increase cardiac output during periods of increased metabolic demands is impaired. RAAS activation also results in fluid retention, which, in combination with LV diastolic dysfunction, leads to higher LV filling pressures. Heart failure symptoms are due to elevated biventricular filling pressures (dyspnea, abdominal pain) or subnormal cardiac output (fatigue, pallor, and diaphoresis). In addition, peripheral vascular and musculoskeletal changes (endothelial dysfunction, skeletal muscular atrophy, mitochondrial loss) may contribute to exercise-related symptoms and to abnormalities detected during exercise testing [5].

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_22

Exercise Testing in Children with Dilated Cardiomyopathy

A normal cardiopulmonary exercise test (CPET) depends on normal response of the cardiovascular, respiratory, and musculoskeletal systems to exercise. Exercise impairment in children with dilated cardiomyopathy and LV dysfunction may be due to a combination of factors including: inadequate tissue O_2 delivery resulting from impaired heart rate and/or stroke volume response, abnormalities in the distribution or impedance of blood flow in the pulmonary and peripheral circulation, and skeletal muscle changes associated with deconditioning. CPET is useful in quantifying the degree of impairment in these systems and determining the mechanism of a patient's symptoms. CPET is often normal in children with mild LV dysfunction. With progression of LV dysfunction, patients may not report an increase in symptoms, as they learn to self-limit their activities. CPET may help in identifying exercise limitations in these patients as they develop moderate and severe LV dysfunction. CPET may also be useful in risk-stratification of children with severe LV dysfunction and in the serial assessment of exercise performance in these children.

Oxygen Consumption During Exercise

Given the close relationship between oxygen consumption ($\dot{V}_{O2}$) and cardiac output, the impairment in peak $\dot{V}_{O2}$ in children with LV dysfunction is a common finding. It is usually reported in children as percentage of predicted value for age and gender and implies an impaired ability to increase cardiac output with exercise. This should be further differentiated as to whether it is due to limited heart rate increase (such as with submaximal effort, sinus node disease, or beta blocker therapy) or limited stroke volume increase.

Because peripheral oxygen extraction at peak exercise is similar in health and disease states, oxygen pulse ($\dot{V}_{O2}$ divided by heart rate) at peak exercise is proportional to the stroke volume at peak exercise. Low peak O_2 pulse is therefore interpreted as impaired stroke volume increase with exercise. Patients with a limited ability to augment stroke volume with exercise rely on a rise in heart rate to augment their cardiac output. This results in an abnormally steep slope of the heart rate increase relative to the $\dot{V}_{O2}$ increase.

During CPET, the rate of rise in carbon dioxide production from lactate release starts earlier than in healthy individuals, resulting in reduced ventilatory anaerobic threshold (VAT). The $\dot{V}_{O2}$–work rate (WR) slope, measured during cycle ergometer testing, may also be abnormal in these subjects with a less steep slope ($\dot{V}_{O2}/\Delta WR$) as WR increases.

Ventilatory Abnormalities

Patients with LV dysfunction begin to develop metabolic acidosis at lower WR compared to normal subjects and have lower VAT. This leads to increase in minute ventilation to maintain arterial H^+ homeostasis. In addition, CPET often shows evidence of ventilation/perfusion mismatch with increased dead space volume and reduced gas exchange efficiency. In some patients, exercise is associated with periodic breathing (exercise oscillatory ventilation), a finding that is associated with higher filling pressures and low cardiac output [6]. Despite these ventilation abnormalities, their exercise limitation is due to impaired cardiac output reserve and not ventilation, and they have ample, often high breathing reserve at peak exercise.

Patients with impaired gas exchange efficiency have a greater ventilatory response for the same amount of expired CO_2 and an above-normal $\dot{V}_E/\dot{V}_{CO2}$ slope. This is caused by pulmonary blood flow maldistribution and ventilation/perfusion mismatch in patients with LV dysfunction. When assessing $\dot{V}_E/\dot{V}_{CO2}$ slope, one must take into account the fact that the slope is higher in healthy children and reaches normal adult values only around 16 years of age [7, 8].

Blood Pressure and Electrocardiography Response

A blunted blood pressure (BP) response to exercise in dilated cardiomyopathy is usually a late finding and suggests an inability to increase cardiac output with exercise. It has been associated with adverse outcomes in both adults and in children with dilated cardiomyopathy [9, 10]. Continuous electrocardiography (EKG) monitoring during CPET is important for assessing heart rate response during exercise (the rate of increase and peak rate) and to detect exercise-induced arrhythmias during exercise and in recovery.

Cardiopulmonary Exercise Testing as a Prognostic Tool

Two exercise variables—peak $\dot{V}_{O2}$ and the $\dot{V}_E/\dot{V}_{CO2}$ slope—have been shown to stratify adults in heart failure for 1-year survival. Exercise testing became an important component of heart transplant evaluation in adults after Mancini et al. reported ~50% 1-year mortality in heart failure patients with peak $\dot{V}_{O2} < 14$ ml/kg/min managed medically. In contrast, patients with equally severe LV dysfunction but with peak $\dot{V}_{O2} \geq 14$ ml/kg/min had 94% 1-year survival with medical management [11]. Peak $\dot{V}_{O2}$ was later shown to be superior to clinical and hemodynamic variables in predicting transplant-free survival [12]. Because beta blockers reduce mortality in heart failure while potentially reducing peak heart rate response during exercise, peak $\dot{V}O_2 < 10$–12 ml/kg/min or <50% predicted are the accepted thresholds associated with poor outcome in adults on these medications [13–15]. $\dot{V}_E/\dot{V}_{CO2}$ slope >34 has also been associated with higher mortality and a 3-year survival of 57% [16].

For children in heart failure, a peak $\dot{V}_{O2} < 50\%$ predicted for age and sex is a Class I indication for listing for transplantation [17]. This recommendation was initially based on expert consensus and extrapolation from adult data but has been supported by a study of children who underwent CPET during their heart transplant evaluation. The authors found that children with biventricular circulation and peak $\dot{V}O_2 < 50\%$ predicted were at 4.7-fold higher risk of death or deterioration on follow-up compared with those with peak $\dot{V}_{O2} \geq 50\%$ predicted. $\dot{V}_E/\dot{V}_{CO2}$ slope ≥34 was associated with a 2.7-fold increase in risk for adverse outcomes in subjects with biventricular circulation (Figs. 22.1 and 22.2) [18]. A higher $\dot{V}_{O2}$ threshold (<63%) was reported to be the discriminator between children with good and poor outcomes in a UK study but included DCM children with near-normal function [19]. The interpretation was

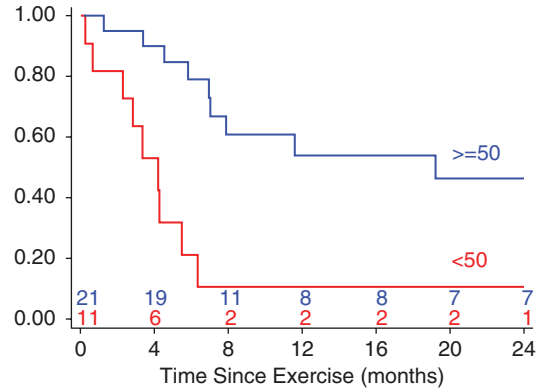


Fig. 22.1 Freedom from death or deterioration stratified by percent-predicted peak oxygen consumption ($\dot{V}_{O2}$) in children with biventricular circulation. (Reprinted with permission from [18])

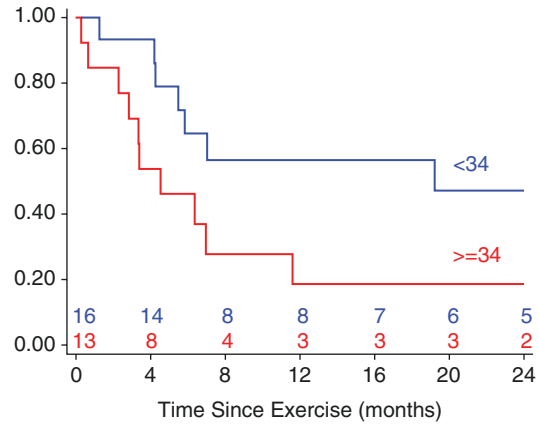


Fig. 22.2 Freedom from death or deterioration stratified by minute ventilation ($\dot{V}_E$)/carbon dioxide production ($\dot{V}_{CO2}$) slope in children with biventricular circulation. (Reprinted with permission from [18])

therefore confounded by LV function and provided outcome data in children with mild vs. severe LV dysfunction rather than outcome differences based on $\dot{V}_{O2}$ among children with equally severe LV dysfunction.

6-Minute Walk Test

The 6-minute walk test is easier to perform than CPET and may be used if a child is unable to perform CPET. Poor performance on the 6-minute walk test is associated with mortality in adults with chronic heart failure [20, 21]. In a small pediatric study in children with DCM, a 6-minute walk distance <63% predicted was associated with a 2-year transplant-free survival of 73% vs. 92% in children with a 6-minute walk distance ≥63% predicted [22]. These results were also confounded by the severity of LV dysfunction as children with very mild dysfunction were included in the study. The test differentiated outcomes among children with mild vs. severe LV dysfunction rather than among children with equally severe LV dysfunction.

In summary, the objective measurement of exercise performance (by either a CPET or when not feasible a 6-minute walk test) is a valuable tool in assessing cardiac reserve in children with dilated cardiomyopathy. Although large, prospective studies are lacking, the existing literature supports the usefulness of these tests in assessing risk, establishing prognosis, and in decision making for timing of advanced therapies such as listing for heart transplant.

Prototypical Patient

The patient was a 19-year-old adolescent female who was diagnosed with a Stage 4 neuroblastoma at 2 years of age. This condition was treated successfully with surgery and a chemotherapeutic regimen that included Adriamycin at a dose of 200 mg/m^2. Subsequently, she did very well until 14 years of age when she was diagnosed with ventricular tachycardia and ventricular dysfunction after presenting with an irregular heartbeat on a routine school physical. The ventricular tachycardia was effectively controlled with ablation procedures and antiarrhythmic medications. However, her LV function never recovered and in fact declined progressively. At the time of the exercise test, the echocardiographically determined LV ejection fraction was 37%. A CPET using a cycle ergometer with a 15 W/min was obtained to further assess her current status (Table 22.1 and Fig. 22.3). At the time of the test she was being treated with captopril, mexiletene, and carvedilol.

Her peak $\dot{V}_{O2}$, peak work rate, and $\dot{V}_{O2}$ at the VAT were severely depressed. Based upon the O_2 pulse data, an inability to increase the stroke volume to appropriate levels at peak exercise was the primary factor responsible for these abnormalities. The heart rate increased excessively during exercise (despite the beta-blocker therapy), as her cardiovascular system attempted to compensate for the depressed stroke volume. No significant ectopy was detected. The $\dot{V}_E/\dot{V}_{CO2}$ slope was slightly high and the end-tidal pCO_2 during exercise slightly low consistent with

Table 22.1 Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	14.6
Peak $\dot{V}_{O2}$ (%predicted)	41
Peak work rate (W)	72
Peak work rate (%predicted)	52
Peak RER	1.22
Peak O_2 pulse (%predicted)	47
Peak heart rate (bpm)	172
Peak heart rate (%predicted)	88
Heart rate increase	Excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	28
$\dot{V}_E/\dot{V}_{CO2}$ slope	29
End-tidal pCO_2 at VAT (mm Hg)	37
End-tidal pCO_2 during exercise	Slightly low
Forced vital capacity (%predicted)	78
FEV1 (%predicted)	69
FEF 25–75 (%predicted)	48
Blood pressure response	Blunted

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

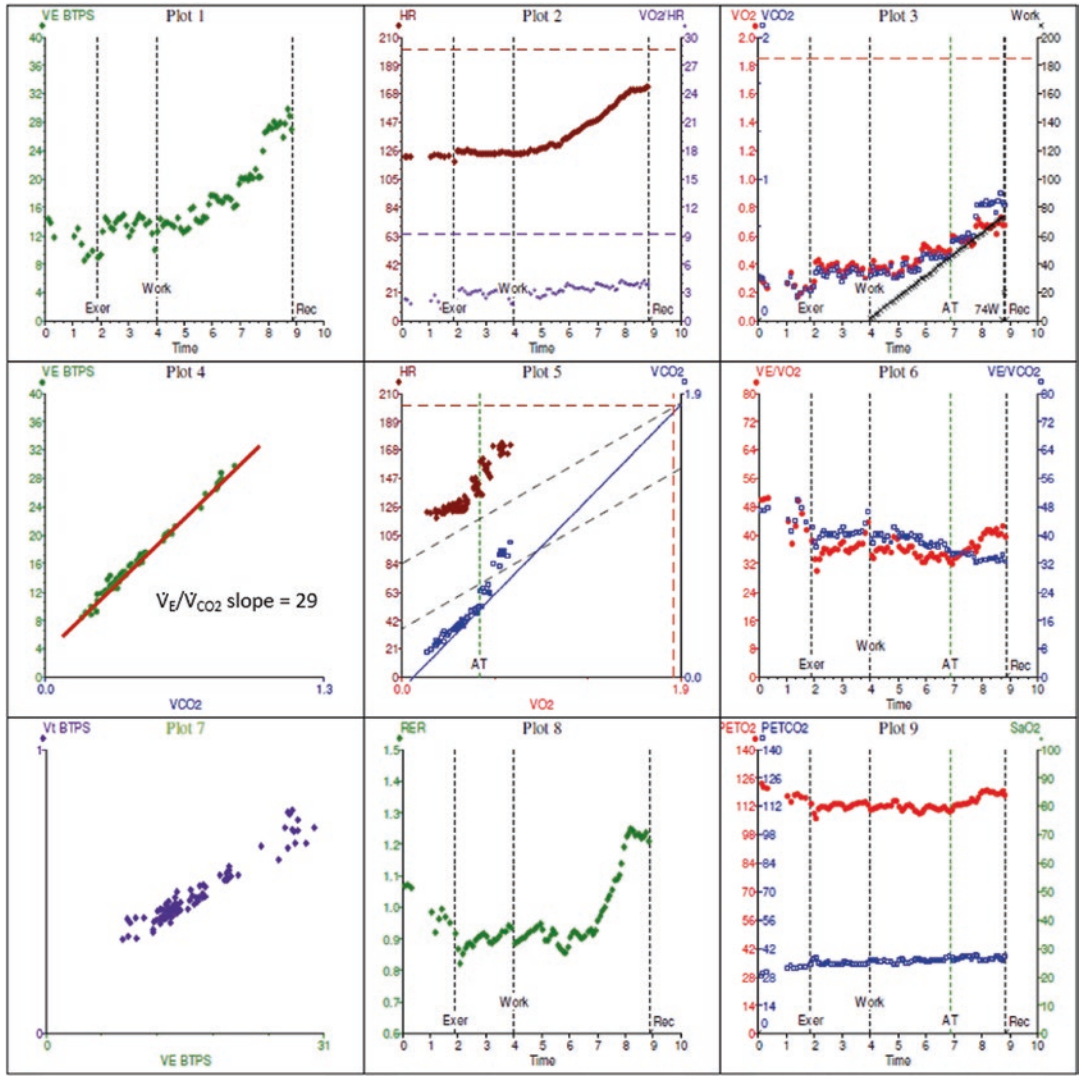


Fig. 22.3 9-panel graph from cardiopulmonary exercise test of prototypical patient. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, PETCO2 end tidal pCO2, PETO2 end tidal pO2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, V_{O2} oxygen consumption, V_{O2}/HR oxygen pulse

mildly inefficient gas exchange during exercise likely secondary to the ventilation/perfusion mismatch that results from elevated LV end diastolic pressure. The obstructive pattern present on her baseline spirometry may also have been related to elevated LV end diastolic pressure. The results of this study were a major influence on a subsequent decision to refer the patient for a heart transplant.

References

1. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA. 2006;296(15):1867–76.
2. Jefferies JL, Towbin JA. Dilated cardiomyopathy. Lancet. 2010;375(9716):752–62.
3. Singh RK, Canter CE, Shi L, Colan SD, Dodd DE, Everitt MD, et al. Survival without cardiac

transplantation among children with dilated cardiomyopathy. J Am Coll Cardiol. 2017;70:2663–73.
4. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure. J Am Coll Cardiol Img. 2011;4(1):98–108.
5. Zizola C, Schulze PC. Metabolic and structural impairment of skeletal muscle in heart failure. Heart Fail Rev. 2013;18(5):623–30.
6. Murphy RM, Shah RV, Malhotra R, Papagiannopoulos PP, Hough SS, Systrom DM, et al. Exercise oscillatory ventilation in systolic heart failure. An indicator of impaired hemodynamic response to exercise. Circulation. 2011;124:1442–51.
7. Nagano y BR, Kuraishi K, Yasuda T, Ikoma M, Nishibata K, et al. Ventilatory control during exercise in normal children. Pediatr Res. 1998;43(5):704–7.
8. Marinov B, Kostianev S, Turnovska T. Ventilatory efficiency and rate of perceived exertion in obese and non-obese children performing standardized exercise. Clin Physiol Funct Imaging. 2002;22:254–60.
9. Sinagra G, Iorio A, Merlo M, Cannata A, Stolfo D, Zambon E, et al. Prognostic value of cardiopulmonary exercise testing in idiopathic dilated cardiomyopathy. Int J Cardiol. 2016;223:596–603.
10. Chen CK, Manlhiot C, Russell JL, Kantor PF, McCrindle BW, Conway J. The utility of cardiopulmonary exercise testing for the prediction of outcomes in ambulatory children with dilated cardiomyopathy. Transplantation. 2017;101(10):2455–60.
11. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83:778–86.
12. Myers J, Gullestad L, Vagelos R, Do D, Bellin D, Ross H, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. Ann Intern Med. 1998;129:286–93.
13. Peterson LR, Schechtman KB, Ewald GA, Geltman EM, Meyer T, Krekeler P, et al. The effect of beta-adrenergic blockers on the prognostic value of peak exercise oxygen uptake in patients with heart failure. J Heart Lung Transplant. 2003;22:70–7.
14. O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. Circulation. 2005;111:2313–8.
15. Stelken AM, Younis LT, Jennison SH, Miller DD, Miller LW, Shaw LJ, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. J Am Coll Cardiol. 1996;27:345–52.
16. Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chua TP, Davos CH, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation. 2001;103:967–72.
17. Canter CE, Shaddy RE, Bernstein D, Hsu DT, Chrisant MR, Kirklin JK, et al. Indications for heart transplantation in pediatric heart disease: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;115(5):658–76.
18. Lytrivi ID, Blume ED, Rhodes J, Dillis S, Gauvreau K, Singh TP. Prognostic value of exercise testing during heart transplant evaluation in children. Circ Heart Fail. 2013;6:792–9.
19. Giardini A, Fenton M, Andrews RE, Derrick G, Burch M. Peak oxygen uptake correlates with survival without clinical deterioration in ambulatory children with dilated cardiomyopathy. Circulation. 2011;124:1713–8.
20. Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD investigators. JAMA. 1993;270(14):1702–7.
21. Passantino A, Lagioia R, Mastropasqua F, Scrutinio D. Short-term change in distance walked in 6 min is an indicator of outcome in patients with chronic heart failure in clinical practice. J Am Coll Cardiol. 2006;48(1):99–105.
22. Den Boer SL, Flipse DHK, van der Meulen MH, Backx AP, du Marchie Sarvaas GJ, Ten Harkel AD, et al. The 6-minute walk test as a predictor for outcome in children with dilated cardiomyopathy and chronic stable heart failure. Pediatr Cardiol. 2017;38(3):465–71.

Hypertrophic Cardiomyopathy

23

Renee Margossian and Jonathan Rhodes

Basic Anatomy and Physiology

Hypertrophic cardiomyopathy (HCM) is a condition characterized by a nondilated and hypertrophied left ventricle (LV), in the absence of a physiologic derangement that may account for the observed increased wall thickness (e.g., aortic valve stenosis or systemic hypertension). Physiologic hypertrophy related to intense physical activity, so-called athlete's heart, is also excluded from the diagnosis of HCM. The clinical expression and natural history of this disorder are widely variable [1].

In adult cohorts, the etiology of HCM is thought to be due to mutations in sarcomeric genes in 85–90% of cases, with pathogenic variants reported for almost all of the sarcomeric proteins. A large majority of these cases are due to variants in MYBPC3 and MYH7 genes (70% of identified mutations), with other genes (TNNT2, TNNI3, TPM1, MYL2, MYL3, and ACTC1) involved at a much lower frequency (1–5% each) [2]. However, the etiologic basis of the disease is broader in the pediatric age range [3]. Potential etiologies include multisystem syndromic disorders such as Noonan syndrome and Friedrich ataxia and metabolic/mitochondrial disorders such as Pompe disease and MELAS (*m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*troke-like episodes).

At a tissue level, HCM is characterized by myofiber disarray with interstitial and subendocardial myocardial fibrosis. The result of myofiber disarray is cellular hypertrophy, due to the isometric contraction of randomly positioned cells. In fact, the regions with the most hypertrophy typically demonstrate the greatest degree of disarray [1].

Echocardiograms in patients with HCM demonstrate varying anatomic phenotypes, in addition to left ventricle hypertrophy (LVH). The hypertrophy itself ranges from mild to severe and most frequently involves the basal anterior septum and the adjacent free wall segment, although any segment may be affected [4]. Dynamic left ventricular outflow tract obstruction (LVOTO) is a common association, and is due to a combination of systolic anterior motion of the mitral valve apparatus, and its apposition with the thickened ventricular septum. Distortion of the mitral apparatus may also result in clinically significant mitral regurgitation [1].

Although LV systolic function is typically normal or supranormal, diastolic dysfunction is a common association and may be responsible for many of the exercise-related symptoms in HCM. Indeed, left atrial size, a primary indicator

R. Margossian (✉) · J. Rhodes
Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Department of Pediatrics, Harvard Medical School, Boston, MA, USA
e-mail: Renee.margossian@cardio.chboston.org; jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_23

of diastolic dysfunction, has been correlated with exercise intolerance in children and adolescents with HCM [5].

Although the overall life expectancy for patients with HCM can be near normal, a majority of patients (especially older patients) experience symptoms. These include chest pain, exertional dyspnea, palpitations, and syncope. A minority of patients die suddenly (annual incidence of ~0.5–1% per year), which may be the initial manifestation of the disease. The highest incidence of sudden cardiac death (SCD) in HCM appears to be in the third and fourth decades of life [1].

Exercise Hemodynamics in Hypertrophic Cardiomyopathy

The vast majority of patients with HCM have experienced exercise limitations and decreased functional capacity by late adulthood. While many young patients are asymptomatic, formal exercise testing can reveal significant, clinically important abnormalities that may not be recognized or appreciated by the patient or his/her family. Cardiopulmonary exercise testing (CPET) typically focuses upon the patient's rhythm, blood pressure response, and peak $\dot{V}_{O2}$. Other indices—such as the O_2 pulse, $\dot{V}_E/\dot{V}_{CO2}$ slope, end-tidal pCO_2, and anaerobic threshold—can provide additional insights into the patient's cardiopulmonary function and how it is affected by his/her cardiac disease.

The pathophysiology of the exercise limitations in HCM is complex, with interwoven etiologies. These include LV diastolic dysfunction, LVOTO, and chronotropic incompetence [6]. A variable amount of deconditioning secondary to exercise restrictions and/or exercise-related symptoms is also frequently present. Systolic dysfunction and congestive heart failure are rare, particularly in the pediatric age range, affecting less than 5% of patients; however, when this end-stage or "burned-out" phase occurs, exercise limitations and their mechanisms are similar to patients with systolic heart failure due to other causes.

When exercise dysfunction is present, an inability to increase stroke volume (either measured or reflected by a low O_2 pulse at peak exercise) is usually responsible for limited exercise capacity and is closely tied to LV diastolic dysfunction. In a study of 156 adult patients with HCM, Finocchiaro and colleagues found that 39% had reduced exercise tolerance; 19% also had elevated $\dot{V}_E/\dot{V}_{CO2}$ slopes. Peak cardiac index, peak stroke volume, and the E/E' ratio were strongly related to peak $\dot{V}_{O2}$. Peak $\dot{V}_{O2}$, left atrial volume, and the $\dot{V}_E/\dot{V}_{CO2}$ slope were also independently associated with a combined clinical endpoint of death, heart transplant, or clinical deterioration leading to septal reduction [7]. Other studies have reported similar findings [8]. The $\dot{V}_E/\dot{V}_{CO2}$ slope elevation is probably a reflection of the elevated left-sided filling pressures and consequent impairment of pulmonary gas exchange during exercise (see Chap. 12).

Invasive studies during exercise have also shown an inverse correlation between time to peak filling at peak exercise and cardiopulmonary indices, suggesting that LV diastolic function during exercise is related to peak $\dot{V}_{O2}$ and peak cardiac output [9].

In addition to diastolic dysfunction, LVOTO can also play a role in the reduced stroke volume response to exercise. Moreover, LVOTO can contribute to a physiologically disadvantageous loop, with LVOTO leading to increased mitral regurgitation, increased hypertrophy, and decreased LV compliance, all resulting in elevated left atrial and pulmonary venous pressures [10]. In a study of 135 patients with HCM, 25% of whom had LVOTO, there was an inverse relationship between LV outflow gradient and peak $\dot{V}_{O2}$, and patients undergoing septal ablation and surgical myectomy for LVOTO have demonstrated improvements in peak $\dot{V}_{O2}$ after the procedures [11–13].

The combination of LVOTO (and consequent increased myocardial oxygen consumption) and an impaired cardiac output during exercise may result in insufficient coronary blood flow and an imbalance between myocardial oxygen supply and demand during exercise. Coronary microvascular dysfunction and/or myocardial bridging also may be present in some patients with HCM and may further contribute to this problem [1, 14]. This imbalance, along with the myocardial fibrosis present in some patients with HCM, probably underlies

the increased risk for exercise-related arrhythmias and sudden death in patients with HCM.

Chronotropic incompetence, or blunting of the exercise-induced rise in heart rate, is another factor that can contribute to the exercise intolerance of patients with HCM. Although the exact mechanism is not known, altered beta-receptor function, impaired calcium signaling, and/or fibrosis in the region of the sinoatrial node are thought to play roles [15]. In a study of 68 patients with HCM (age 44.8 ± 14.6 years) Efthimiadis and colleagues reported that chronotropic incompetence—defined as failure to reach a chronotropic index of 0.8—was present in half of the patients [16]. A high prevalence of abnormal sinus node function (66%) and His-Purkinje conduction (30%) was also noted in a cohort of 155 HCM patients who underwent invasive electrophysiology studies [17]. Possible explanations for these findings include myocardial disarray or overt fibrotic changes in the atrial myocardium. In fact, in a study of 98 patients assessed with both cardiac magnetic resonance imaging (MRI) and symptom-limited exercise testing, the presence of delayed gadolinium enhancement (a marker of myocardial fibrosis) was an independent predictor of exercise capacity [18].

Clinical Value of Exercise Testing in Hypertrophic Cardiomyopathy

In light of the proven efficacy of prophylactic implantable defibrillators [1, 19], and the value of surgical relief of LVOTO in selected patients [20], the assessment of an HCM patient's risk for sudden death risk constitutes an important part of the management of the HCM patient. This assessment is based on a composite of clinical markers. A fall in systolic blood pressure (SBP) >20 mm Hg during exercise is a parameter that is included in the composite as a Class IIa recommendation [21]. The hypotensive blood pressure response to exercise has a low positive but high negative predictive accuracy, indicating it is most useful for identifying patients who are at lower risk for sudden death [22]. An abnormal blood pressure response to exercise is nevertheless considered a risk factor for sudden death in HCM, particularly in patients younger than 40 years and in patients with a family history of sudden death [23, 24]. When associated with a significant LVOTO at rest or with exercise, it may be an indication for surgical and/or other interventions.

During upright exercise, systolic blood pressure typically increases by at least 20 mm Hg from rest to peak exercise [25]. However, approximately one-third of patients with HCM fail to augment their SBP or experience a fall in SBP [26]. This abnormal SBP response to exercise may be due to a failure to augment cardiac output and/or stroke volume during exercise, the development of LVOTO, or the development of myocardial ischemia. Abnormal activation of ventricular mechanoreceptors may also be involved [27]. These receptors may be activated by the stretch of the myocardium, causing vasodilation. Regional variations in stretch result from the myofiber disarray and fibrosis, which lead to regions of increased wall stress.

Characterization of a patient's LVOTO during exercise also has important clinical implications. Approximately 1/3 of HCM patients have LVOTO >30 mm Hg at rest, and another 1/3 develop significant LVOTO during exercise. In patients without significant exertional symptoms, a provocable gradient >50 mm Hg has been found to predict clinical deterioration and symptom progression to New York Heart Association (NYHA) functional class III/IV [28, 29]. Development of LVOTO rapidly at lower levels of exercise is associated with more impairment in functional capacity compared to later onset of gradient [28]. In addition, for patients with severe symptoms but without significant LVOTO at rest, the detection of a large exercise-induced gradient identifies a therapeutic target that may be amenable to medical treatment (e.g., beta-blockers), surgical myectomy, or alcohol septal ablation. Effective relief of LVOTO can improve symptoms and provide a survival benefit [20]. In medication-refractory patients, septal myectomy (or alcohol septal ablation in older adolescents and adults) provides effective symptomatic improvement, with up to 95% of patients improving to NYHA class I or II [21]. However, in those patients with severe medication-refractory symptoms who do not have a provocable gradient, management is confined to cardiac transplantation.

These observations underscore the principle that therapeutic interventions such as surgical myectomy, etc. should not be confined to patients with large resting gradients and in fact should be considered for all severely symptomatic patients with LVOTO, including those with physiologically provocable gradients [20, 28]. Serial exercise testing should also be employed to objectively assess the effectiveness of any therapeutic intervention.

Several studies with large numbers of patients with HCM have demonstrated that CPET data can improve the management of patients with HCM and assist clinicians attempting to estimate a patient's risk for sudden death, heart failure death, and heart transplantation [7, 30, 31]. As discussed previously, a low peak $\dot{V}_{O2}$ and an elevated $\dot{V}_E/\dot{V}_{CO2}$ slope are risk factors for death, heart transplant, or clinical deterioration [8]. A decreased peak $\dot{V}_{O2}$ also provides an independent and quantitative assessment of functional limitation in the setting of an ambiguous personal history. Although functional capacity in cardiovascular disease is typically assessed by NYHA classification, in many patients with HCM, this classification system may be misleading. One study of 135 HCM patients reported that 99% had peak $\dot{V}_{O2}$ less than 80% predicted for age, gender, and size [32]. While peak $\dot{V}_{O2}$ did correlate with NYHA class, there was considerable overlap, and even class I patients had a high incidence of reduced peak $\dot{V}_{O2}$ (70%).

Peak $\dot{V}_{O2}$ data can also help guide decisions regarding referral for cardiac transplantation. In a report of 1005 patients with HCM (median follow-up of 5.5 years), a peak $\dot{V}_{O2}$ of less than 50% predicted was associated with overall mortality and sudden cardiac death equivalent events—such as resuscitated sudden death and appropriate automatic implantable cardioverter defibrillator (AICD discharge) [33]. Numerous cross-sectional studies have also correlated peak $\dot{V}_{O2}$ with various clinically relevant variables including diastolic dysfunction [9], quality of life [34], and LVOT gradients [35].

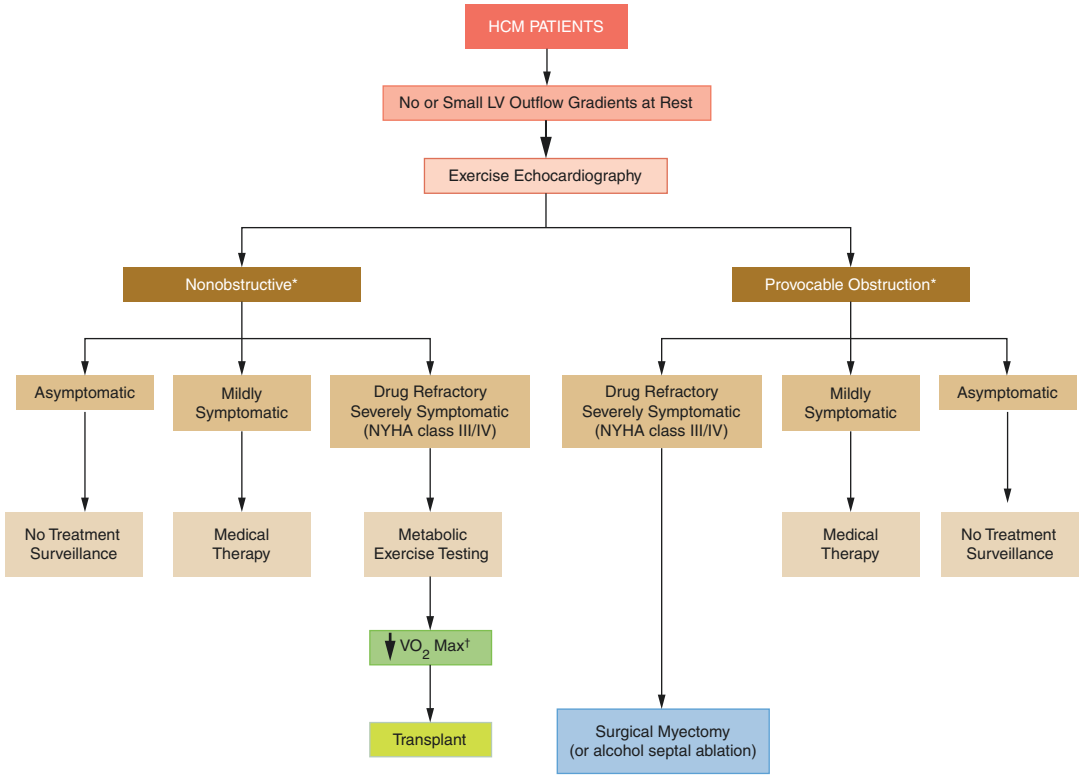


Fig. 23.1 Algorithm summarizing applications of exercise testing to diagnose and manage hypertrophic cardiomyopathy. (Reprinted with permission from [28])

The detection of exercise-induced arrhythmias also has important clinical implications. In patients with HCM, exercise-induced ventricular arrhythmias have been found to be associated with a 3.73-fold increase in the risk of subsequent sudden cardiac death and/or AICD discharge [36, 37]. The manner in which exercise test data may be integrated into the clinical management of patients with HCM is illustrated in Fig. 23.1 [28].

Because of the risk of sudden death during exercise, patients with HCM are generally restricted from most competitive sports [38]. However, the benefits of moderate levels of exercise have recently been gaining increased recognition/appreciation. For an individual patient with HCM, the substantial benefits of these activities must be weighed against the risks. Exercise test data may help in this assessment. For HCM patients without concerning risk factors and with reassuring exercise test data, many clinicians will conclude that the risk/benefit ratio for moderate exercise is favorable. Maintaining good hydration and avoiding adverse environmental conditions (e.g., hot or cold weather, high humidity) can also mitigate the risks of exercise [1, 39, 40].

Risks Associated with Exercise Testing

As recently as 2002, the American College of Cardiology/American Heart Association guidelines for exercise testing cautioned clinicians against exercise testing in HCM patients due to a concern for development of hypotension and/or severe LVOTO that could lead to arrhythmias or cardiovascular collapse [41]. However, considerable data have shown that exercise testing is feasible and safe when performed in a monitored, controlled, and supervised clinical setting [42–44]. A Cleveland Clinic series of 263 (mostly adult) HCM patients reported a major complication in <0.04% (1 patient; sustained VT requiring cardioversion) and minor events in 23%, including mild chest pain (10.2%), severe chest pain (1.5%), new nonsustained atrial arrhythmias (3.0%), nonsustained ventricular arrhythmias (4.2%), and presyncope (12.9%), with many patients experiencing >1 minor event. A decrease in SBP ≥20 mm Hg was noted in 6.1%. There were no syncopal events, and patients with minor events had higher LVOTO gradients after exercise and those without minor events [44].

In our review of arrhythmias during exercise tests performed at Boston Children's Hospital between 2013 and 2016, we found that 147 tests were performed for patients with HCM (excluding patients with positive genetic testing and no clinical phenotype). On two (1.4%) occasions, serious arrhythmias requiring CPR and defibrillation and/or cardioversion developed. One patient developed hemodynamically marginal, relatively slow ventricular tachycardia at minimal exercise. The other patient developed ventricular fibrillation during the exercise test. Fortunately, both were quickly and effectively resuscitated and experienced no identifiable neurological injury. Moreover, the exercise tests results significantly influenced the patients' subsequent management. The first patient was listed for and underwent successful cardiac transplantation (partly on the basis of the exercise test result). The second was referred for resection of subaortic stenosis.

Hence, in our experience, exercise testing in pediatric patients with HCM does carry significant risk. However, the data acquired during the exercise test can have a dramatic impact upon the patient's management, and the risks associated with exercise testing can certainly be mitigated by having appropriate staff and equipment available at the test. The value of acquiring exercise test data in a controlled environment where prompt, effective interventions can be administered, if necessary, must be weighed against the risks of the exercise test, and the risks of overlooking a potentially life-threatening medical condition. In many cases, the risk/benefit ratio of exercise testing is probably favorable, but the test should be eschewed if the exercise data is unlikely to be helpful or to change the patient's management [45].

Prototypical Patient

The patient was a 22-year-old man who presented for evaluation of episodes of dizziness and syncope with exercise. His physical examination was normal except for moderate obesity (body mass index 36.3). No murmurs were detected, even

with the Valsalva maneuver. His electrocardiogram (EKG) was remarkable for T wave inversions in I, aVL, V5, and V6. His baseline transthoracic echocardiogram revealed mild septal hypertrophy, hyperdynamic LV function, mild chordal systolic anterior motion (SAM), mild mitral regurgitation, and decreased septal tissue Doppler diastolic velocities. (Of note, the EKG and echocardiographic abnormalities were new and were not present on studies obtained 2 years earlier when he was evaluated for similar, albeit milder symptoms.) He also performed an exercise test on a treadmill, using the standard Bruce Protocol (Table 23.1). He developed his typical dizziness at peak exercise, requiring test termination. His endurance time, peak $\dot{V}_{O2}$ and $\dot{V}_{O2}$ at the ventilatory anaerobic threshold (VAT) were low-normal. His $\dot{V}_E/\dot{V}_{CO2}$ slope and heart rate response to exercise were normal. He had mild systolic hypertension at rest. His SBP rose modestly during the early stages of exercise, but plateaued thereafter and fell precipitously immediately post-exercise, in association with his symptoms. No ectopy was detected during the study, but he did develop 1–2 mm of ST depression with additional T wave inversions in the inferior leads at higher levels of exercise. Post-exercise stress echocardiography revealed severe LVOTO (Fig. 23.2) with hyperdynamic LV function and marked chordal SAM.

Table 23.1 Selected data from cardiopulmonary exercise test, pre-beta-blocker therapy

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	27.8
Peak $\dot{V}_{O2}$ (%predicted)	88
Endurance time (percentile)	25–50th
Peak RER	1.12
Peak O2 pulse (%predicted)	87
Peak heart rate (bpm)	179
Peak heart rate (%predicted)	90
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	41
Arterial oxygen saturation	Normal
$\dot{V}_E/\dot{V}_{CO2}$ slope	25
End-tidal pCO_2 at VAT (mm Hg)	44
End-tidal pCO_2 during exercise	Normal
Spirometry	Normal
Blood pressure response	Blunted; precipitous drop post-exercise

RER Respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

Following this study, he was started on beta-blocker therapy and instructed to avoid strenuous physical activities and return for re-evaluation and a repeat stress test in 1 month. At his follow-up visit, he reported

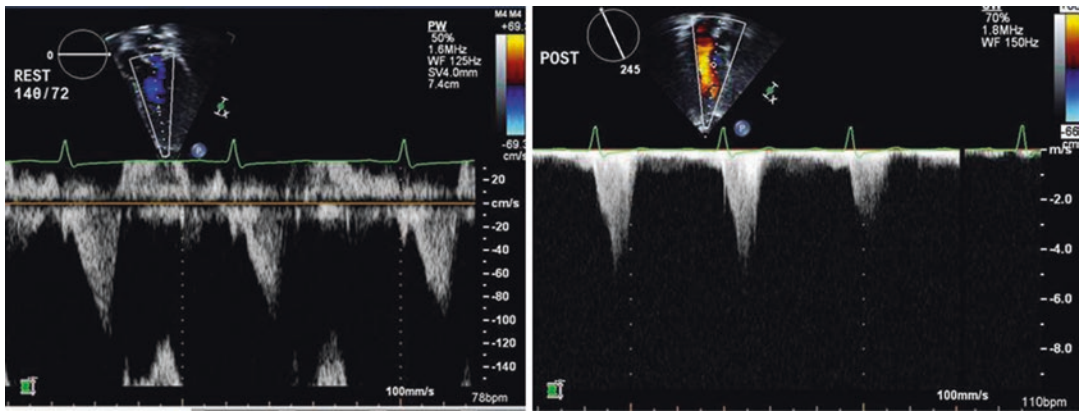


Fig. 23.2 Left ventricular outflow tract (LVOT) Doppler measurements from the prototypical patient's initial stress echocardiogram, at rest (left) and post-exercise (right). Although there was no significant LVOT gradient at rest, the post-exercise gradient exceeded 100 mm Hg

that his symptoms had resolved. On the exercise test (Table 23.2), he did not develop dizziness. His endurance time and peak $\dot{V}_{O2}$ were similar. His VAT was higher. His peak heart rate was lower and his oxygen pulse correspondingly higher. No additional ST changes developed during exercise. His blood pressure response to exercise was normal and did not decline precipitously post-exercise. No LVOTO gradient was detectable at rest or at peak exercise (Fig. 23.3).

Table 23.2 Selected data from cardiopulmonary exercise test, post-beta-blocker therapy

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	25.8
Peak $\dot{V}_{O2}$ (%predicted)	83
Endurance time (percentile)	25–50th
Peak RER	1.22
Peak O2 pulse (%predicted)	126
Peak heart rate (bpm)	130
Peak heart rate (%predicted)	66
V̇O2 at VAT (% of predicted peak V̇O2)	63
Arterial oxygen saturation	Normal
V_E/V_{CO2} slope	25
End-tidal pCO_2 at VAT (mm Hg)	44
End-tidal pCO_2 during exercise	Normal
Spirometry	Normal
Blood pressure response	Blunted; precipitous drop post-exercise

RER Respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

This case illustrates how exercise can produce dramatic LVOTO in patients, even when no significant obstruction is present at rest. The obstruction can be associated with hypotension and additional ST abnormalities and symptoms. In this patient, the beta-blocker therapy reduced heart rate and thereby allowed the heart to fill more during diastole. The medication also impeded the increase in contractility that is associated with exercise. These hemodynamic effects combined to increase LV diastolic and systolic volumes during exercise and effectively eliminated the dynamic subaortic obstruction that had developed during exercise prior to the initiation of the medication. They also resulted in a dramatic improvement in the patient's symptoms.

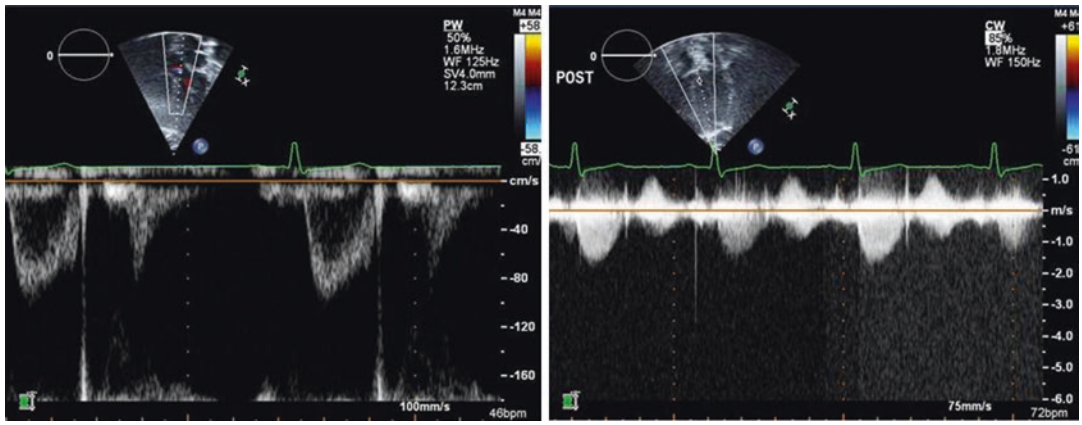


Fig. 23.3 Left ventricular outflow tract (LVOT) Doppler measurements from the prototypical patient's stress echocardiogram following the initiation of beta-blocker therapy. There was no LVOT gradient at rest (left) or post-exercise (right)

References

1. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med. 2018;379(7):655–68.
2. Sabater-Molina M, Perez-Sanchez I, Hernandez Del Rincon JP, Gimeno JR. Genetics of hypertrophic cardiomyopathy: a review of current state. Clin Genet. 2018;93(1):3–14.
3. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. Circulation. 2007;115(6):773–81.
4. Shapiro LM, McKenna WJ. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a two-dimensional echocardiographic study. J Am Coll Cardiol. 1983;2(3):437–44.
5. Menon SC, Ackerman MJ, Cetta F, O'Leary PW, Eidem BW. Significance of left atrial volume in patients <20 years of age with hypertrophic cardiomyopathy. Am J Cardiol. 2008;102(10):1390–3.
6. Patel V, Critoph CH, Elliott PM. Mechanisms and medical management of exercise intolerance in hypertrophic cardiomyopathy. Curr Pharm Des. 2015;21(4):466–72.
7. Finocchiaro G, Haddad F, Knowles JW, Caleshu C, Pavlovic A, Homburger J, et al. Cardiopulmonary responses and prognosis in hypertrophic cardiomyopathy: a potential role for comprehensive noninvasive hemodynamic assessment. JACC Heart Fail. 2015;3(5):408–18.
8. Magri D, Santolamazza C. Cardiopulmonary exercise test in hypertrophic cardiomyopathy. Ann Am Thorac Soc. 2017;14(Supplement_1):S102–S9.
9. Lele SS, Thomson HL, Seo H, Belenkie I, McKenna WJ, Frenneaux MP. Exercise capacity in hypertrophic cardiomyopathy. Role of stroke volume limitation, heart rate, and diastolic filling characteristics. Circulation. 1995;92(10):2886–94.
10. Arshad W, Duncan AM, Francis DP, O'Sullivan CA, Gibson DG, Henein MY. Systole-diastole mismatch in hypertrophic cardiomyopathy is caused by stress induced left ventricular outflow tract obstruction. Am Heart J. 2004;148(5):903–9.
11. Ruzyllo W, Chojnowska L, Demkow M, Witkowski A, Kusmierczyk-Droszcz B, Piotrowski W, et al. Left ventricular outflow tract gradient decrease with non-surgical myocardial reduction improves exercise capacity in patients with hypertrophic obstructive cardiomyopathy. Eur Heart J. 2000;21(9):770–7.
12. Redwood DR, Goldstein RE, Hirshfeld J, Borer JS, Morganroth J, Morrow AG, et al. Exercise performance after septal myotomy and myectomy in patients with obstructive hypertrophic cardiomyopathy. Am J Cardiol. 1979;44(2):215–20.
13. Firoozi S, Elliott PM, Sharma S, Murday A, Brecker SJ, Hamid MS, et al. Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy. A comparison of clinical, haemodynamic and exercise outcomes. Eur Heart J. 2002;23(20):1617–24.
14. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Thorac Cardiovasc Surg. 2011;142(6):e153–203.
15. Luo HC, Dimaano VL, Kembro JM, Hilser A, Hurtado-de-Mendoza D, Pozios I, et al. Exercise heart rates in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2015;115(8):1144–50.
16. Efthimiadis GK, Giannakoulas G, Parcharidou DG, Pagourelias ED, Kouidi EJ, Spanos G, et al. Chronotropic incompetence and its relation to exercise intolerance in hypertrophic cardiomyopathy. Int J Cardiol. 2011;153(2):179–84.
17. Fananapazir L, Tracy CM, Leon MB, Winkler JB, Cannon RO 3rd, Bonow RO, et al. Electrophysiologic abnormalities in patients with hypertrophic cardiomyopathy. A consecutive analysis in 155 patients. Circulation. 1989;80(5):1259–68.
18. Romero-Puche A, Marin F, Gonzalez-Carrillo J, Garcia-Honrubia A, Climent V, Feliu E, et al. Gadolinium-enhanced cardiovascular magnetic resonance and exercise capacity in hypertrophic cardiomyopathy. Rev Esp Cardiol. 2008;61(8):853–60.
19. Maron BJ, Spirito P. Implantable defibrillators and prevention of sudden death in hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2008;19(10):1118–26.
20. Maron BJ, Dearani JA, Ommen SR, Maron MS, Schaff HV, Gersh BJ, et al. The case for surgery in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;44(10):2044–53.
21. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;124(24):2761–96.
22. Olivotto I, Montereggi A, Mazzuoli F, Cecchi F. Clinical utility and safety of exercise testing in patients with hypertrophic cardiomyopathy. G Ital Cardiol. 1999;29(1):11–9.
23. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36(7):2212–8.
24. Authors/Task Force members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733–79.

25. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. Circulation. 1997;96(9):2987–91.
26. Thaman R, Elliott PM, Shah JS, Mist B, Williams L, Murphy RT, et al. Reversal of inappropriate peripheral vascular responses in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46(5):883–92.
27. Counihan PJ, Frenneaux MP, Webb DJ, McKenna WJ. Abnormal vascular responses to supine exercise in hypertrophic cardiomyopathy. Circulation. 1991;84(2):686–96.
28. Rowin EJ, Maron BJ, Olivotto I, Maron MS. Role of exercise testing in hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2017;10(11):1374–86.
29. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114(21):2232–9.
30. Magri D, Re F, Limongelli G, Agostoni P, Zachara E, Correale M, et al. Heart failure progression in hypertrophic cardiomyopathy- possible insights from cardiopulmonary exercise testing. Circ J. 2016;80(10):2204–11.
31. Coats CJ, Rantell K, Bartnik A, Patel A, Mist B, McKenna WJ, et al. Cardiopulmonary exercise testing and prognosis in hypertrophic cardiomyopathy. Circ Heart Fail. 2015;8(6):1022–31.
32. Sharma S, Elliott P, Whyte G, Jones S, Mahon N, Whipp B, et al. Utility of cardiopulmonary exercise in the assessment of clinical determinants of functional capacity in hypertrophic cardiomyopathy. Am J Cardiol. 2000;86(2):162–8.
33. Masri A, Pierson LM, Smedira NG, Agarwal S, Lytle BW, Naji P, et al. Predictors of long-term outcomes in patients with hypertrophic cardiomyopathy undergoing cardiopulmonary stress testing and echocardiography. Am Heart J. 2015;169(5):684–92 e1.
34. Huff CM, Turer AT, Wang A. Correlations between physician-perceived functional status, patient-perceived health status, and cardiopulmonary exercise results in hypertrophic cardiomyopathy. Qual Life Res. 2013;22(3):647–52.
35. Cannon RO 3rd, McIntosh CL, Schenke WH, Maron BJ, Bonow RO, Epstein SE. Effect of surgical reduction of left ventricular outflow obstruction on hemodynamics, coronary flow, and myocardial metabolism in hypertrophic cardiomyopathy. Circulation. 1989;79(4):766–75.
36. Cheung CC, Laksman ZW, Mellor G, Sanatani S, Krahn AD. Exercise and inherited arrhythmias. Can J Cardiol. 2016;32(4):452–8.
37. Gimeno JR, Tome-Esteban M, Lofiego C, Hurtado J, Pantazis A, Mist B, et al. Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. Eur Heart J. 2009;30(21):2599–605.
38. Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NA 3rd, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 3: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis: a scientific statement from the American Heart Association and American College of Cardiology. Circulation. 2015;132(22):e273–80.
39. Hindieh W, Adler A, Weissler-Snir A, Fourey D, Harris S, Rakowski H. Exercise in patients with hypertrophic cardiomyopathy: a review of current evidence, national guideline recommendations and a proposal for a new direction to fitness. J Sci Med Sport. 2017;20(4):333–8.
40. Gregor P. Hypertrophic cardiomyopathy and sports. Cor Vasa. 2015;57:e12–e5.
41. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (committee to update the 1997 exercise testing guidelines). J Am Coll Cardiol. 2002;40(8):1531–40.
42. Argulian E, Chaudhry FA. Stress testing in patients with hypertrophic cardiomyopathy. Prog Cardiovasc Dis. 2012;54(6):477–82.
43. Morise AP. Exercise testing in nonatherosclerotic heart disease: hypertrophic cardiomyopathy, valvular heart disease, and arrhythmias. Circulation. 2011;123(2):216–25.
44. Drinko JK, Nash PJ, Lever HM, Asher CR. Safety of stress testing in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2004;93(11):1443–4, A12.
45. Barry OM, Gauvreau K, Rhodes J, Reichman JR, Bourette L, Curran T, O'Neill J, Pymm JL, Alexander ME. Incidence and predictors of clinically important and dangerous arrhythmias during exercise tests in pediatric and congenital heart disease patients. JACC Clin Electrophysiol. 2018;4(10):1319–27.

Coronary Anomalies

24

Jennifer Huang and Keri M. Shafer

Basic Anatomy and Physiology

Normal anatomy includes three coronary arteries: left anterior descending, left circumflex, and right coronary artery. The right coronary supplies the posterior descending branch in the majority of patients (Fig. 24.1) [1]. The primary function of the coronary arteries is to provide blood flow (and oxygen) in quantities sufficient to support the metabolic needs of the myocardium. This function is maximally stressed when the metabolic needs of the myocardium are greatest, i.e, during exercise. To fulfill this function, the coronary arteries must be unobstructed and provided with blood flow under sufficient pressure, with adequate oxygenation. The coronary arteries must also drain into a normal microvascular bed that serves the entire myocardium.

J. Huang
Exercise Physiology, Ambulatory and Outreach Services, Department of Pediatrics, Doernbecher Children's Hospital, Oregon Health and Science University, Portland, OR, USA
e-mail: huangje@ohsu.edu

K. M. Shafer (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
e-mail: Keri.Shafer@cardio.chboston.org

The clinical diagnosis of myocardial ischemia is based on the concept of "the ischemic cascade"—a physiological construct that postulates that signs of myocardial ischemia will be detectable on myocardial perfusion imaging and echocardiography before they produce electrocardiographic (EKG) changes or symptoms (Fig. 24.2) [2]. This concept was developed based on experience in patients with atherosclerotic coronary artery disease (CAD)—a condition that produces intraluminal obstructions of the epicardial coronary arteries and constitutes the most common type of CAD in adults. Consequently, exercise stress testing with EKG monitoring ± myocardial perfusion imaging or stress echocardiography has become an integral part of the management of patients for the detection of ischemia.

Intraluminal coronary artery obstruction is a mechanism of myocardial ischemia that may be encountered in some pediatric patients with CAD (e.g., Kawasaki's disease). A pediatric cardiologist may, however, encounter a variety of congenital, acquired, and postoperative conditions that can affect the structure and function of the coronary arteries by mechanisms other than acquired intraluminal obstruction. For instance, patients with anomalous aortic origin of a coronary artery (AAOCA) may have a stenotic origin, intramural course, or an inter-arterial course subject to external compression by the great arteries as they dilate during exercise. In patients with a coronary artery fistula, ischemia may be

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_24

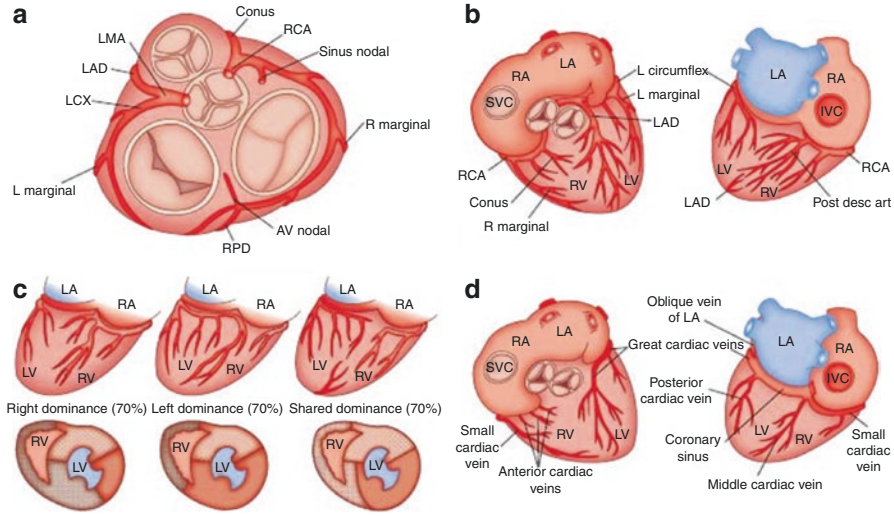


Fig. 24.1 Figure from Moss and Adam's Heart disease (citation). (**a**) Aortic origins of normal coronary arteries shown at the level of the base. (**b**) anterior and posterior views of the coronary arteries. (**c**) Perfusion of the posterior wall determines coronary dominance. 70% of patients perfuse the posterior wall via the right coronary artery. (**d**) Anterior and posterior depiction of the coronary venous anatomy)

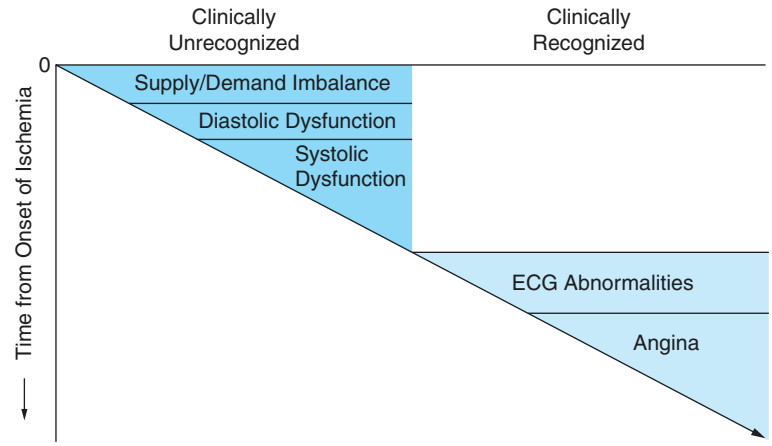


Fig. 24.2 The ischemic cascade. ECG electrocardiograph. (Reprinted with permission from [2])

produced by the physiologically obligate steal phenomenon that can compromise blood flow to the myocardium fed by the affected coronary artery. In patients with cardiac transplant vasculopathy secondary to chronic rejection, abnormalities of the coronary microvasculature may be responsible for, or contribute to, the myocardial ischemia [3]. The relationship between ischemia and exercise-induced abnormalities in myocardial perfusion imaging, echocardiography and EKG tracings may have a different tempo in pediatric patients with these conditions, and it is unclear whether the "ischemic cascade" concept that has been found to be so useful in the diagnosis and management of typical adult atherosclerotic CAD applies with equal validity to these anatomically and physiologically distinct conditions. It is possible that in pediatrics, there may be a lag time between the cellular level ischemia and detectible systolic dysfunction. Moreover, experience with exercise testing for these comparatively rare pediatric disorders is

limited, and the data regarding the clinical value of exercise testing is often inconclusive [4].

Anatomic assessments of coronary anatomy in pediatrics typically begin with echocardiography as the proximal portion of the coronary is the most likely affected segment. Additional anatomic data may be acquired, when necessary, with coronary angiography, either invasively during a cardiac catheterization or noninvasively with cardiac computed tomography (CT) or cardiac magnetic resonance imaging (MRI). Occasionally, intravascular ultrasound, optical coherence tomography, and fractional flow reserve may also be employed. For some lesions, clinical decisions may be made solely on the basis of anatomic evaluations, along with knowledge of the natural history of the condition. In other cases, an assessment of coronary artery function is required. Depending upon the nature of the lesion, data from the pediatric exercise physiology laboratory can sometimes be helpful in this regard.

Unfortunately, only limited data is available regarding the clinical value of exercise testing in the majority of the coronary anomalies that may be encountered in pediatrics. Nevertheless, many of the major guidelines recommend screening exercise testing for risk stratification [5, 6].

Diagnosis of Ischemia

Ischemia is the greatest concern for patients with coronary artery anomalies and the primary purpose of exercise testing. Signs of ischemia during a standard exercise test include ST segment and T wave changes on the exercise EKG, angina, hypotension, or ventricular arrhythmias. EKG changes suggestive of ischemia include ST depressions, T wave inversions, or ST elevations in anatomically contiguous leads (Fig. 24.3). Although sensitivity and specificity for ischemia is decreased in pediatrics due to the low pre-test probability of ischemia, adult standards are used. Ischemia is likely in adult exercise testing when there is ST segment depression that is flat or downsloping, more than 1 mm in magnitude, lasting for 0.08 sec or 0.06 sec beyond the J point in 2 contiguous leads and in 3 consecutive beats. Isolated T wave inversion probably carries little clinical significance, but when associated with ST depression is suggestive of coronary artery disease. Anginal symptoms and poor exercise function increase the likelihood that observed ST changes are associated with CAD. Pre-test ST changes decrease the reliability of ST changes during exercise [7].

During stress echocardiography, diastolic and systolic dysfunction can occur. Typically, systolic dysfunction occurs with regional wall motion abnormalities (hypokinesis or akinesis) in the area perfused by the dysfunctional coronary artery. With nuclear perfusion or stress MRI, abnormalities in perfusion can also be seen. As discussed previously, based upon the ischemic cascade concept, nuclear perfusion and stress MRI have the potential to detect ischemia at the earliest time point. However, given the cost, logistics, and time considerations of these tests, stress EKG or stress echocardiography is more commonly performed.

Anomalous Coronary Artery Origin

Congenital anomalies of the coronary origins are relatively common, occurring approximately in 1.3% of patients undergoing coronary angiography [8]. These anomalies include anomalous origin from the pulmonary arteries, a single coronary artery originating from the aorta and giving rise to all three epicardial coronary arteries, or lesions in which both coronaries originate from the same sinus. Each of these anomalies has variable risk for symptoms and sudden cardiac death, but risk is relative to the type of anatomic variation. Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) and AAOCA of the left coronary from the right coronary sinus confers the greatest risk, especially during exercise (Fig. 24.4) [9–11]. In patients with ALCAPA, perfusion of the left main coronary artery is critically impaired once the pulmonary vascular resistance and pulmonary artery pressures decline postnatally. Myocardial ischemia and infarction typically ensue. Without treatment, it is reported that up to 90% of these infants die within the first year of life. In those who survive, collaterals between the right and left coronary

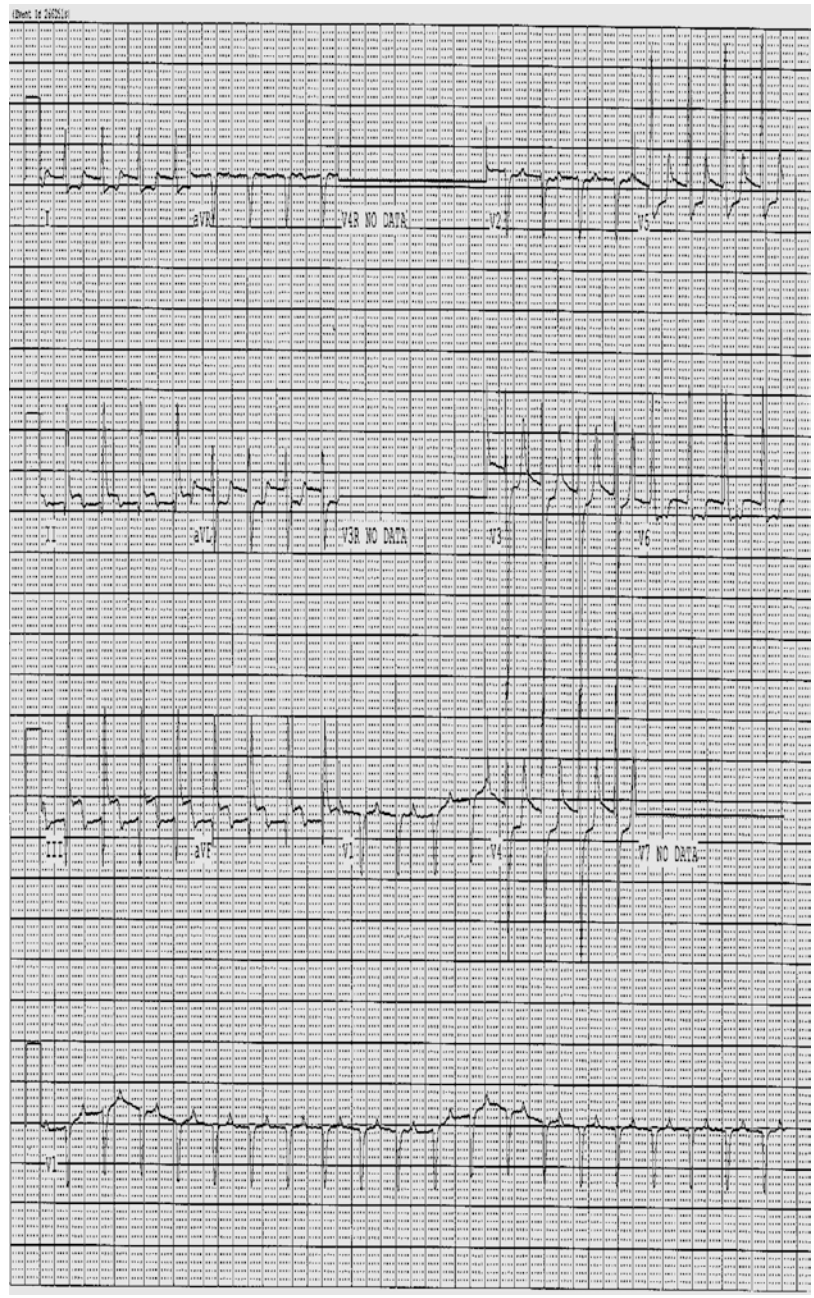


Fig. 24.3 Acute ischemia in the left circumflex coronary artery. There is ST elevation in the inferior leads and ST depression in I, aVL, and the left precordial leads

circulations develop and provide adequate myocardial perfusion. However, the anomalous left coronary artery causes blood to steal away from the myocardial circulation to the pulmonary artery. Those who survive infancy have a high risk for sudden death after the first decade of life but there are reports of patient diagnosed in adulthood [12, 13].

In patients with AAOCA of the left coronary from the right coronary sinus, the orifice and/or the intramural portion of the coronary artery may be stenotic. In addition, the inter-arterial portion of the coronary artery may become compressed between the aorta and pulmonary artery, especially during exercise when systolic pressures (and myocardial oxygen demand) are

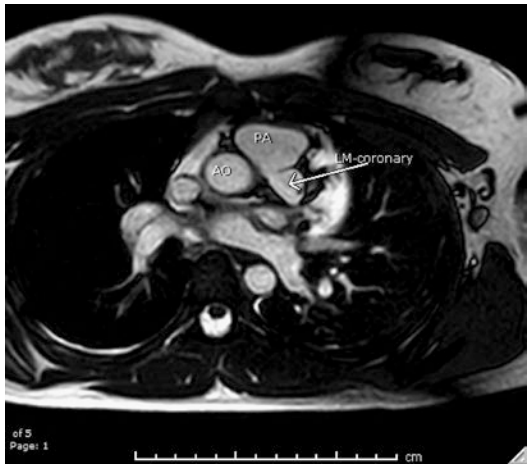


Fig. 24.4 Cardiac magnetic resonance image (MRI) showing a large anomalous left coronary artery arising from the pulmonary artery

higher. It has been estimated that the risk for sudden death in patients with AAOCA of the left coronary from the right coronary sinus is more than tenfold higher than the risk associated with AAOCA of the right coronary from the left coronary sinus [14]. Consequently, surgical intervention is generally recommended for ALCAPA and for AAOCA of the left coronary from the right coronary sinus, regardless of exercise test data.

AAOCA of the right coronary artery from the left sinus is the most common congenital coronary artery anomaly and may be found in 0.17–0.45% of the population [8, 10, 14]. In this anomaly, the right coronary artery usually takes an inter-arterial course (88–100% of cases) [8]. If a coronary artery course is inter-arterial, external compression of the anomalous coronary artery as it travels between the aorta and pulmonary artery can compromise coronary blood flow, particularly during exercise when systolic pressures are higher. However, the vast majority of patients with this condition never develop clinical problems related to this anomaly. Additional anatomic features, such as an acute takeoff angle or slit-like orifice of the coronary artery, may confer increased risk. If these features and/or concerning symptoms (e.g., exertional chest pain or syncope) are present, surgical unroofing of the anomalous coronary artery is probably indicated [14]. Exercise testing is sometimes employed to assess these patients. However, positive studies (either before or after surgery) are rare, and patients who have died have had documented normal stress EKG studies [10]. The clinical value of stress testing for this anomaly therefore remains undefined. Certainly, a strongly positive test, with symptoms, EKG changes, rhythm disturbances, perfusion defects, and/or wall motion abnormalities suggestive of ischemia should motivate intervention in otherwise ambiguous cases. However, patients and families should be reminded of the variable outcomes associated with a negative stress test in anomalous coronary arteries.

Acquired Coronary Artery Disease in Pediatrics

Acquired coronary artery lesions are encountered in Kawasaki's disease (KD), early CAD (often in the setting of familial hypercholesterolemia), and CAD secondary to heart transplants (transplant vasculopathy). Given that 25% of untreated KD patients and 5% treated will develop coronary artery aneurysms, ongoing coronary ischemia and thrombosis risk are common in KD. KD-associated coronary artery ectasia often regresses over time, with 54% in one larger study regressing over a 13.6-year period and 90% of regression occurring within 2 years from disease onset [15]. The likelihood for aneurysm progression is inversely proportional to the initial size of the aneurysm. Highest-risk KD patients include those with bilateral coronary involvement and those with giant aneurysms of 8 mm or greater. Patients with KD-associated coronary artery disease are at risk for coronary artery thromboses and/or stenoses (Fig. 24.5). The physiology of these intraluminal obstructions probably resembles typical adult-type coronary artery disease. Not surprisingly, therefore, the role of exercise stress testing with myocardial perfusion imaging or stress echocardiography in KD has been widely accepted and fairly well established [16, 17].

Transplant vasculopathy commonly develops following heart transplantation and has been found to be a significant risk factor for late graft failure in pediatrics [18]. Vasculopathy may include epicardial as well as microvascular CAD [3]. However, the cardiac allograft is denervated at the time of

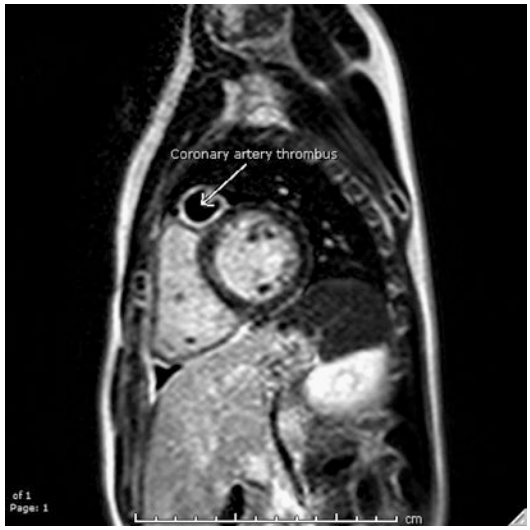


Fig. 24.5 Cardiac magnetic resonance image (MRI) showing large coronary artery thrombus after Kawasaki disease in a giant coronary artery aneurysm

transplantation; consequently typical anginal symptoms usually do not develop. Baseline EKG abnormalities are also common in this population and reduce the value of exercise EKG data. Moreover, probably because the genesis, histology, and biological behavior of the coronary lesions differ from those encountered in typical adult CAD, many have found that the diagnostic reliability of stress-imaging studies is inferior to that encountered in adults with atherosclerotic CAD. Although one study has found stress echocardiography to correlate extremely well with angiographically confirmed epicardial coronary artery disease [19], the results of that study have not been duplicated by other investigators [20, 21].

Postoperative Coronary Artery Assessment After Congenital Heart Surgery

In patients who have undergone the arterial switch procedure for transposition of the great arteries, the coronary arteries are re-implanted into the neo-aortic root. Kinking of the transplanted coronary arteries or scarring at the sites of anastomoses can result in impaired coronary blood flow. The role of exercise testing in this population is discussed in Chap. 19.

Rarely, patients with a repaired dilated pulmonary artery (e.g., patients with repaired tetralogy of Fallot or pulmonary hypertension) may develop myocardial ischemia secondary to compression of the left coronary artery by the dilated pulmonary artery especially as many of these patients have anomalous coronary arteries [22]. These patients often have a wide right bundle branch block, which compromises the reliability of exercise EKG. Experience with stress echocardiography and/or myocardial perfusion imaging in these patients is limited. The considerations relevant to patients with coronary artery problems related to other congenital heart defects probably apply to these patients as well. Once again, a strongly positive test, with symptoms, rhythm disturbances, perfusion defects, and/or wall motion abnormalities suggestive of ischemia should motivate intervention in otherwise ambiguous cases.

Coronary Artery Fistulae

Coronary artery fistulae encompass a range of anomalies in which the circulation bypasses the capillary bed. These connections can occur between the coronary arteries and a multitude of structures including the coronary veins, right heart chambers, atria, or pulmonary vessels. These lesions may be found in 0.13–0.18% of patients undergoing coronary angiography [23]. The left coronary artery system is involved more often than the right (75% versus 25%) [24]. The physiological significance of the malformation is dependent on the shunt size. Small shunts are usually asymptomatic and may regress. Rarely, large fistulae may result in heart failure from left-to-right shunting in infancy [24–26]. Coronary artery fistulae rarely cause myocardial ischemia, as collateral blood flow and coronary artery recruitment usually develop and effectively preserve myocardial perfusion. An exception to this generalization occurs when a thrombus develops within the fistula and results in myocardial ischemia or infarction [27]. Experience with exercise testing in patients with this anomaly is limited. It may be of value in patients with ambiguous symptoms/findings.

References

1. Allen HD, Gutgessel HP, Clark EB, Driscoll DJ, editors. Moss and Adams' heart disease in infants, children, and adolescents: including the fetus and young adult. 6th ed. Philadelphia: Wolters Kluwer; 1993.
2. Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol. 1987;59(7):23c–30c.
3. Kindel SJ, Law YM, Chin C, Burch M, Kirklin JK, Naftel DC, et al. Improved detection of cardiac allograft vasculopathy: a multi-institutional analysis of functional parameters in pediatric heart transplant recipients. J Am Coll Cardiol. 2015;66(5):547–57.
4. Thompson WR. Stress echocardiography in paediatrics: implications for the evaluation of anomalous aortic origin of the coronary arteries. Cardiol Young. 2015;25(8):1524–30.
5. Van Hare GF, Ackerman MJ, Evangelista JA, Kovacs RJ, Myerburg RJ, Shafer KM, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 4: congenital heart disease: a scientific statement from the American Heart Association and American College of Cardiology. Circulation. 2015;132(22):e281–91.
6. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation. 2017;135(17):e927–99.
7. Jones NL. The exercise electrocardiogram. In: Jones NL, editor. Clinical exercise testing. 4th ed. Philadelphia: W. B. Saunders; 1997. p. 109–23.
8. Yamanaka O, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. Catheter Cardiovasc Diagn. 1990;21(1):28–40.
9. Eckart RE, Scoville SL, Campbell CL, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. Ann Intern Med. 2004;141(11):829–34.
10. Basso C, Maron BJ, Corrado D, Thiene G. Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. J Am Coll Cardiol. 2000;35(6):1493–501.
11. Taylor AJ, Rogan KM, Virmani R. Sudden cardiac death associated with isolated congenital coronary artery anomalies. J Am Coll Cardiol. 1992;20(3):640–7.
12. Wesselhoeft H, Fawcett JS, Johnson AL. Anomalous origin of the left coronary artery from the pulmonary trunk. Its clinical spectrum, pathology, and pathophysiology, based on a review of 140 cases with seven further cases. Circulation. 1968;38(2):403–25.
13. Roberts WC. Major anomalies of coronary arterial origin seen in adulthood. Am Heart J. 1986;111(5):941–63.
14. Cheezum MK, Liberthson RR, Shah NR, Villines TC, O'Gara PT, Landzberg MJ, et al. Anomalous aortic origin of a coronary artery from the inappropriate sinus of valsalva. J Am Coll Cardiol. 2017;69(12):1592–608.
15. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation. 1996;94(6):1379–85.
16. Newburger JW, Takahashi M, Burns JC. Kawasaki disease. J Am Coll Cardiol. 2016;67(14):1738–49.
17. Tsuda E, Tsujii N, Hayama Y. Stenotic lesions and the maximum diameter of coronary artery aneurysms in Kawasaki disease. J Pediatr. 2018;194:165–170.e162.
18. Kirk R, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbels F, et al. The registry of the international society for heart and lung transplantation: fourteenth pediatric heart transplantation report—2011. J Heart Lung Transplant. 2011;30(10):1095–103.
19. Chen MH, Abernathey E, Lunze F, Colan SD, O'Neill S, Bergersen L, et al. Utility of exercise stress echocardiography in pediatric cardiac transplant recipients: a single-center experience. J Heart Lung Transplant. 2012;31(5):517–23.
20. Jeewa A, Dreyer WJ, Kearney DL, Denfield SW. The presentation and diagnosis of coronary allograft vasculopathy in pediatric heart transplant recipients. Congenit Heart Dis. 2012;7(4):302–11.
21. Lee MS, Tadwalkar RV, Fearon WF, Kirtane AJ, Patel AJ, Patel CB, et al. Cardiac allograft vasculopathy: a review. Catheter Cardiovasc Interv. 2018;92(7):E527–36.
22. Khante V, Agarwal S, Satyarthi S, Upretti L, Satsangi DK. Compression of the left main coronary artery by a pulmonary artery aneurysm in a patient with tetralogy of fallot and an absent pulmonary valve. J Card Surg. 2011;26(3):330–2.
23. Harle T, Kronberg K, Elsasser A. Coronary artery fistula with myocardial infarction due to steal syndrome. Clin Res Cardiol. 2012;101(4):313–5.
24. Keane JF, Fyler DC. Vascular fistulae. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Saunders; 2006. p. 799–804.
25. Sherwood MC, Rockenmacher S, Colan SD, Geva T. Prognostic significance of clinically silent coronary artery fistulas. Am J Cardiol. 1999;83(3):407–11.
26. Buccheri D, Chirco PR, Geraci S, Caramanno G, Cortese B. Coronary artery fistulae: anatomy, diagnosis and management strategies. Heart Lung Circ. 2018;27(8):940–51.
27. Gowda RM, Vasavada BC, Khan IA. Coronary artery fistulas: clinical and therapeutic considerations. Int J Cardiol. 2006;107(1):7–10.

Metabolic Disorders

25

Jonathan Rhodes

Metabolic disorders are rare, but have interesting and important implications for exercise physiology. The disorders most commonly encountered in the pediatric exercise physiology laboratory can be divided into two categories: mitochondrial defects and glycogen storage diseases. The physiologic consequences of these disorders will now be discussed.

Mitochondrial Defects

Normally, most of the ATP required by the skeletal muscles during exercise is derived from aerobic metabolism. In patients with mitochondrial disorders (of which there are a variety with varying clinical manifestations), however, the ability of the mitochondria to take up oxygen and generate ATP via oxidative phosphorylation is impaired. This defect may result in a number of symptoms, the most prominent of which is exercise intolerance. Other symptoms include muscle weakness and muscle pain [1–5]. Some mitochondrial disorders (e.g., Barth syndrome) may also be associated with myocardial dysfunction [6, 7].

Patients with mitochondrial disorders typically have a low peak $\dot{V}_{O2}$, low peak work rate, very low ventilatory anaerobic threshold (VAT) and $\Delta\dot{V}_{O2}/\Delta WR$ relationship, and low oxygen pulse at peak exercise. These abnormalities are to a large extent due to the mitochondria's inability to take up oxygen normally. Patients therefore have an early and excessive reliance upon anaerobic metabolism for the generation of the ATP required for the mechanical work of exercise. Because oxygen cannot be extracted from the blood by the exercising muscles, the mixed venous oxygen saturation does not fall (and indeed may even rise) during exercise. This phenomenon may be detected by invasive blood sampling or by near-infrared spectroscopy. In addition, noninvasive cardiac output estimates and stress echocardiography will reveal that the stroke volume is normal or, in cases where ventricular dysfunction is present, certainly not as depressed as might be expected based upon the oxygen pulse measurements. This discrepancy arises, of course, on account of the elevated mixed venous oxygen saturation at peak exercise, which undermines the typical, tight relationship between the oxygen pulse and stroke volume at peak exercise [1–7]. Peak

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_25

heart rate tends to be normal, but the rise in the heart rate relative to $\dot{V}_{O2}$ is excessive, reflecting the cardiopulmonary system's attempt to compensate for the impaired oxygen release to the exercising muscles.

Glycogen Storage Diseases

Glycogen storage diseases (GSDs) refer to inborn errors of metabolism in which the breakdown of glycogen to form glucose and consequently the anaerobic metabolism of glucose (glycolysis) is impaired. One of the more common GSDs encountered in the pediatric exercise physiology laboratory is GSD type III (Cori disease), an autosomal recessive disorder caused by a deficiency of a glycogen debranching enzyme. Symptoms typically include exercise intolerance and a predisposition to hypoglycemia [8]. Another defect relevant to the pediatric exercise physiology laboratory is McArdle Disease, also known as myophosphorylase deficiency or GSD type V. Myophosphorylase is the enzyme that catalyzes glycogenolysis (i.e., the phosphorylation of glycogen to glucose-1-phosphate, which then enters the glycolysis pathway) within the muscle cell. GSDs can have profound effects upon exercise physiology. If sufficient glucose is not available to the muscle cell during exercise, or if glycolysis cannot proceed normally, the anaerobically derived ATP upon which the muscle cell depends at higher levels of exercise is not available. In addition, lactic acid, the product of the anaerobic metabolism of glucose, is not produced in normal quantities. The normal decline in the intramuscular pH and consequent right-shifting of the hemoglobin-oxygen dissociation curve at higher levels of exercise therefore do not occur, and the liberation of oxygen from the blood to the muscle is impaired. Hence, oxygen extraction by the muscle, and the muscle's ability to increase oxidative phosphorylation (as it normally does beyond the anaerobic threshold) are constrained [1, 3, 4, 9].

These abnormalities are manifested in the exercise physiology laboratory by a low-respiratory exchange ratio at peak exercise and an absent or hard-to-identify anaerobic threshold, due to the impaired lactic acid formation. Peak $\dot{V}_{O2}$ is also depressed because of the muscle cells' inability to extract oxygen normally from the hemoglobin in the absence of a lactic acidosis. Consequently, the mixed venous oxygen saturation will not fall appropriately—a phenomenon that may be detected by direct measurement via invasive blood sampling or inferred from near-infrared spectroscopy or noninvasive cardiac output measurements. Blood sampling would also reveal abnormally low lactic acid levels at peak exercise. The oxygen pulse at peak exercise is also low because, as with mitochondrial disorders, the elevated mixed venous oxygen saturation at peak exercise undermines the relationship between the oxygen pulse and stroke volume at peak exercise. As with mitochondrial myopathy patients, the heart rate at peak exercise tends to be normal, but the rise in heart rate relative to $\dot{V}_{O2}$ is excessive, reflecting the cardiopulmonary system's attempt to compensate for the impaired oxygen release to the exercising muscles. However, in contrast to patients with mitochondrial disorders, the $\Delta\dot{V}_{O2}/\Delta$WR relationship is not depressed (and may even be high), as an excessive reliance on anaerobic metabolism is not present [1, 3, 4, 9]. See Table 25.1 for comparison of mitochondrial defects and glycogen storage diseases.

Table 25.1 Comparison of mitochondrial defects and glycogen storage diseases

	Mitochondrial	Glycogen storage disease
Peak $\dot{V}_{O2}$	Low	Low
Peak oxygen pulse	Low	Low
VAT	Low	Often indeterminate
RER at peak exercise	High	Low
$\Delta\dot{V}_{O2}/\Delta$Work Rate	Low	Normal or high
Peak heart rate	Normal	Normal
Heart rate increase	Excessive	Excessive
Mixed venous O_2 saturation	High	High

RER respiratory exchange ratio, *VAT* ventilatory anaerobic threshold

Prototypical Patient: Mitochondrial Defect

The patient was a 24-year-old woman with a mitochondrial defect (YARS-2 mutation). This mutation impairs the function of the enzyme mitochondrial tyrosyl-tRNA synthetase and results in defective mitochondrial protein synthesis. Consequently, patients with this condition have reduced availability of mitochondrially encoded subunits that are required for the normal assembly and function of several of the respiratory chain complex components (complex I, III, and IV). The mitochondria of patients with this condition are unable to take up oxygen from the blood normally and are prone to metabolic acidosis and severe skeletal muscle weakness [10]. At the time of the cardiopulmonary exercise test (CPET) (Table 25.2 and Fig. 25.1), the patient had a normal echocardiogram and a normal hemoglobin/hematocrit. The CPET was performed to further characterize her physiologic status. A cycle ergometer with a 10 W/min ramp was employed for the study.

Her peak work rate and peak $\dot{V}_{O2}$ were extremely low, despite achieving an unusually high respiratory exchange ratio (RER) (1.39). Her VAT was also quite low, and occurred while pedaling against 0 resistance. Her peak heart rate was normal, and her heart rate increase was far out of proportion to her $\dot{V}_{O2}$ during exercise. Her O_2 pulse at peak exercise was quite depressed, as was her $\Delta\dot{V}_{O2}/\Delta$Work Rate. Stress echocardiography revealed normal ventricular function at rest and immediately post-exercise. Near-infrared spectroscopy measurements suggested a paradoxical increase in mixed venous oxygen saturation during exercise.

Table 25.2 Selected data from cardiopulmonary exercise test on patient with mitochondrial disorder

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	14.6
Peak $\dot{V}_{O2}$ (%predicted)	36
Peak work rate (W)	46
Peak work rate (%predicted)	22
Peak RER	1.39
Peak O_2 pulse (%predicted)	39
Peak heart rate (bpm)	169
Peak heart rate (%predicted)	93
Heart rate increase during exercise	Excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	23
$\Delta\dot{V}_{O2}/\Delta$Work Rate (ml/min/W)	6.1
Blood pressure response	Low-normal
Breathing reserve (%)	63

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

In this case, the low peak $\dot{V}_{O2}$ and O_2 pulse were almost certainly due to an inability to extract oxygen from the blood during exercise, rather than an inability to augment stroke volume normally. The low VAT and $\Delta\dot{V}_{O2}/\Delta$Work Rate were due to the impaired aerobic ATP production by the muscles' mitochondria, and a consequent early and excessive reliance upon anaerobic metabolism to generate the ATP required for muscular work. The excessive rise in heart rate developed as a consequence of homeostatic mechanisms (e.g., increased sympathetic stimulation) that attempted to compensate for the inability to extract oxygen from the blood during exercise. The high breathing reserve reflected the patient's inability to raise her metabolic rate.

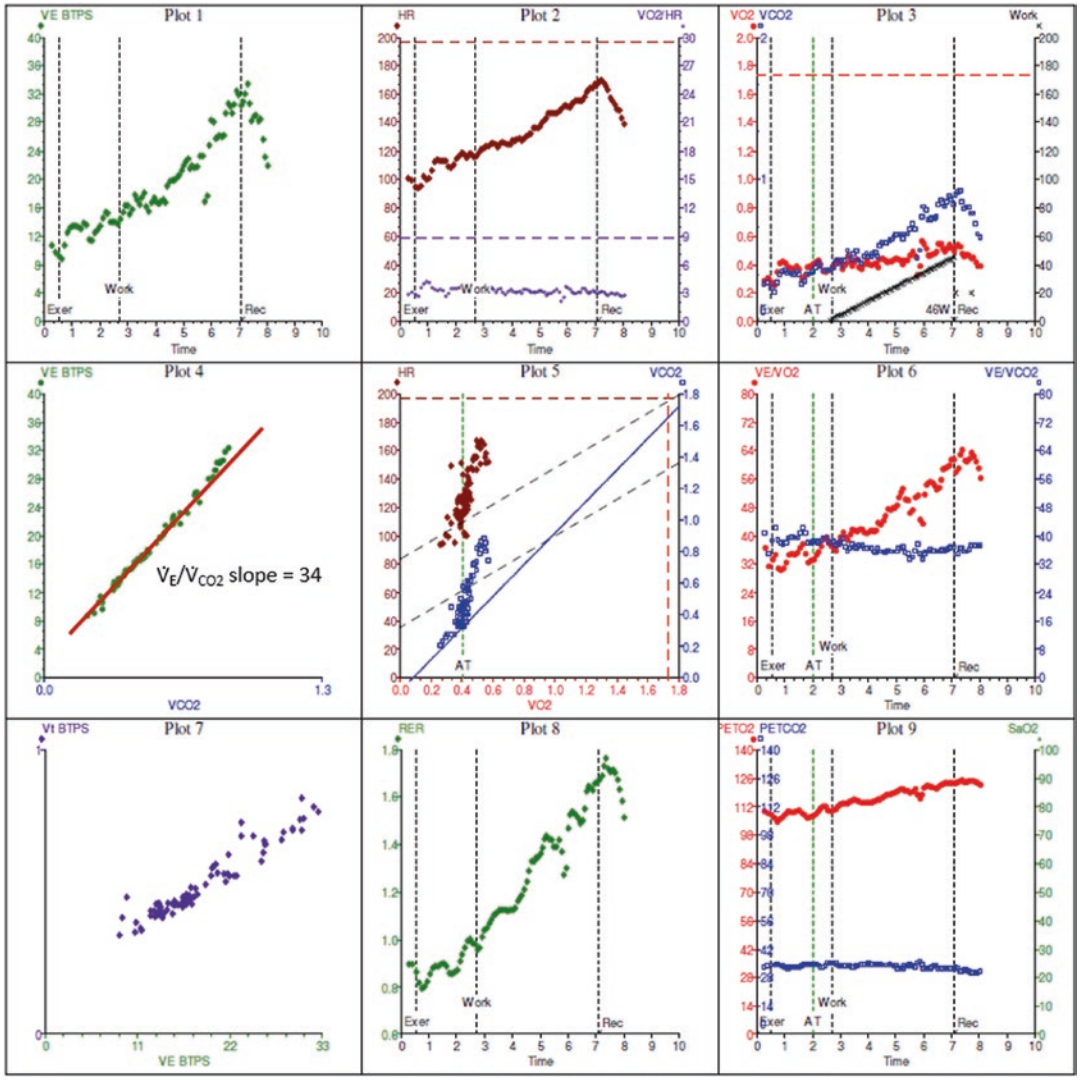


Fig. 25.1 9-panel graph from cardiopulmonary exercise test of prototypical patient with a mitochondrial defect. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, $PETCO_2$ end-tidal pCO_2, $PETO_2$ end-tidal pO_2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, $\dot{V}_{O2}$ oxygen consumption, V_{O2}/HR oxygen pulse

Prototypical Patient: Glycogen Storage Disease

The patient was a 19-year-old adolescent male with glycogen storage disease type III (Cori disease) [8]. He suffered from exercise intolerance and a CPET was performed to better assess his functional status and to serve as a baseline for comparison for future studies obtained to assess the response to various dietary therapies (Table 25.3 and Fig. 25.2). A cycle ergometer with a 20 W/min ramp was employed. An echocardiogram performed at the time of the CPET revealed normal cardiac anatomy and function.

The patient's peak $\dot{V}_{O2}$ and peak work rate were moderate-severely depressed. The poor exercise function appeared to be due to an inability to increase the O_2 pulse normally during exercise. Despite expending a good effort, reflected by a normal peak heart rate as well as subjective observations, the patient's RER did not rise above ~0.9. A VAT was not readily identifiable. The heart rate increase was out of proportion to the increase in $\dot{V}_{O2}$ during exercise. Stress echocardiography was normal, and near-infrared spectroscopy measurements suggested a paradoxical increase in mixed venous oxygen saturation during exercise.

In this case, the low peak $\dot{V}_{O2}$ and O_2 pulse were, once again, not due to an inability to augment stroke volume during exercise. Rather, the enzymatic defect impeded the generation of lactic acid at higher levels of exercise. The physiologically important rightward shift of the hemoglobin-oxygen dissociation curve that normally occurs in the acidic environment generated by lactic acid accumulation within the exercising muscles therefore did not occur. The failure of the RER to rise normally, the inability to detect a VAT, the normal stress echocardiogram, and the increase in mixed venous oxygen saturation all support this proposed physiology. Once again, the excessive rise in heart rate developed as a consequence of homeostatic mechanisms attempting to compensate for the inability to extract oxygen from the blood during exercise. The high breathing reserve reflected the patient's inability to raise his metabolic rate.

Table 25.3 Selected data from cardiopulmonary exercise test on patient with glycogen storage disease

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	23.7
Peak $\dot{V}_{O2}$ (%predicted)	54
Peak work rate (W)	166
Peak work rate (%predicted)	60
Peak RER	0.89
Peak O2 pulse (%predicted)	57
Peak heart rate (bpm)	176
Peak heart rate (%predicted)	95
Heart rate increase during exercise	Excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	Indeterminate
Δ(Delta)$\dot{V}_{O2}$/Δ(Delta)Work Rate (ml/min/W)	9.4
Blood pressure response	Normal
Breathing reserve (%)	74

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

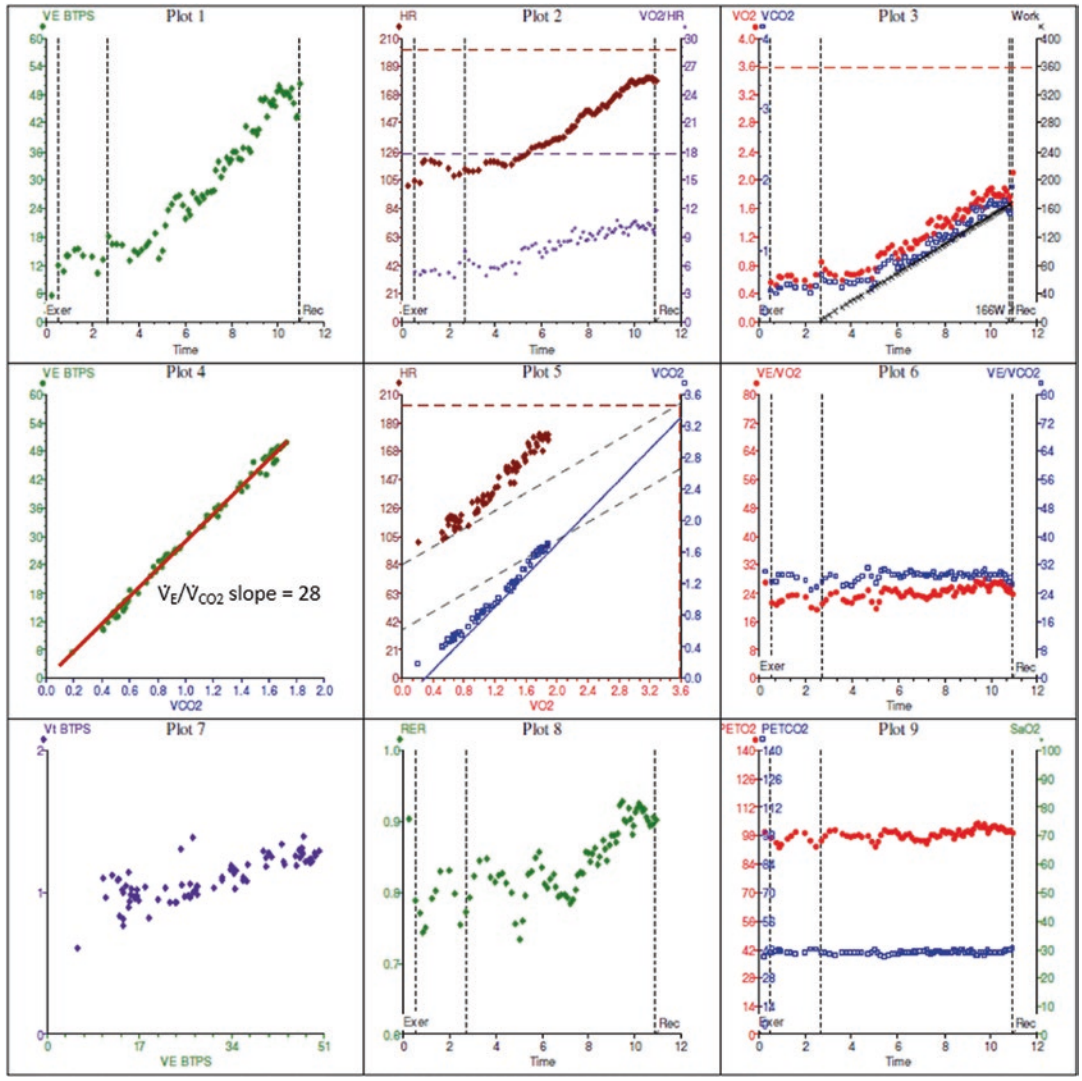


Fig. 25.2 9-panel graph from cardiopulmonary exercise test of prototypical patient with a glycogen storage disease. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, $PETCO_2$ end-tidal pCO_2, $PETO_2$ end-tidal pO_2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, $\dot{V}_{O2}$ oxygen consumption, $\dot{V}_{O2}$/HR oxygen pulse

References

1. Riley MS, Nicholls DP, Cooper CB. Cardiopulmonary exercise testing and metabolic myopathies. Ann Am Thorac Soc. 2017;14(Supplement_1):S129–39.
2. Taivassalo T, Jensen TD, Kennaway N, DiMauro S, Vissing J, Haller RG. The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients. Brain. 2003;126(Pt 2):413–23.
3. Tarnopolsky M. Exercise testing in metabolic myopathies. Phys Med Rehabil Clin N Am. 2012;23(1):173–86, xii.
4. Volpi L, Ricci G, Orsucci D, Alessi R, Bertolucci F, Piazza S, et al. Metabolic myopathies: functional evaluation by different exercise testing approaches. Musculoskelet Surg. 2011;95(2):59–67.
5. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun XG, et al. Principles of exercise testing and interpretation. 5th ed. Philadelphia: Lippincott Williams &Wilkins; 2012. p. 486–92.
6. Bashir A, Bohnert KL, Reeds DN, Peterson LR, Bittel AJ, de Las Fuentes L, et al. Impaired cardiac and skeletal muscle bioenergetics in children, adolescents, and young adults with Barth syndrome. Physiol Rep. 2017;5(3):1–12.

7. Spencer CT, Byrne BJ, Bryant RM, Margossian R, Maisenbacher M, Breitenger P, et al. Impaired cardiac reserve and severely diminished skeletal muscle O(2) utilization mediate exercise intolerance in Barth syndrome. Am J Physiol Heart Circ Physiol. 2011;301(5):H2122–9.
8. Dagli A, Sentner CP, Weinstein DA. Glycogen storage disease type III. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. GeneReviews((r)). Seattle: University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle; 1993.
9. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun XG, et al. Principles of exercise testing and interpretation. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 479–82.
10. Riley LG, Cooper S, Hickey P, Rudinger-Thirion J, McKenzie M, Compton A, et al. Mutation of the mitochondrial tyrosyl-tRNA synthetase gene, YARS2, causes myopathy, lactic acidosis, and sideroblastic anemia—MLASA syndrome. Am J Hum Genet. 2010;87(1):52–9.

Exercise Testing After Pediatric Heart Transplantation

26

Arene Butto and T. P. Singh

Heart transplantation is an established therapy in children with end-stage heart failure. Ten percent of all current heart transplant (HT) surgeries are performed in children <18 years of age. Approximately 25% of pediatric HT recipients are infants <1 year old and the remaining are distributed equally in age groups 1–10 years and 11–17 years [1]. Overall, 45% of pediatric HT recipients have an underlying diagnosis of congenital heart disease and 45% have cardiomyopathy. Advances in perioperative care and immune suppression during the last 2 decades have resulted in progressive improvement in early posttransplant survival. The current median survival in pediatric HT recipients exceeds 15 years and is >20 years in those receiving HT as infants [1].

During the first few months posttransplant, recipients are recovering from deconditioning associated with heart failure; children old enough to participate in a formal cardiac rehabilitation program may benefit from this intervention [2]. HT recipients need lifelong immune suppression. Their quality of life, however, is excellent. Resolution of pretransplant symptoms can be expected in most patients [3]. On long-term follow-up, patients are at risk for hypertension (side effect of medications) and development of coronary artery disease (cardiac allograft vasculopathy), which may affect graft function, exercise tolerance, and survival [4].

Pathophysiology

Transection of sympathetic and parasympathetic nerve fibers during removal of the heart from the donor results in cardiac autonomic denervation in all HT recipients. Lacking vagal tone, HT recipients have a high resting heart rate. They also depend on circulating catecholamines released by the adrenal glands, rather than those released from cardiac sympathetic nerve endings, for heart rate increase during exercise [5]. Approximately 30–35% of HT recipients develop myocardial sympathetic reinnervation over time (3–5 years); 5–8% also develop vagal reinnervation. Sympathetic reinnervation has been associated with improved physiologic responses such as improved myocardial blood flow, ventricular function, and heart rate response during exercise [6, 7].

Although the transplanted heart is structurally normal, it has sustained ischemia-reperfusion injury. Left ventricular (LV) diastolic dysfunction

A. Butto (✉)
Advanced Cardiac Therapies and Cardiac Intensive Care, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: arene.butto@cardio.chboston.org

T. P. Singh
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Heart Failure/Transplant Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: TP.singh@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_26

is common early after HT and improves within months [8]. Persistence of LV diastolic dysfunction, apparent only on fluid challenge, has been described in recipients several years later and may be more common in those with history of rejection or coronary artery disease [9]. The role of LV diastolic dysfunction in causing impaired exercise performance in pediatric HT recipients has been questioned, however. Tissue Doppler imaging and global strain assessment during exercise have demonstrated preserved LV and right ventricular (RV) systolic and diastolic myocardial reserve in pediatric HT recipients [10]. Furthermore, although pediatric HT recipients had smaller LV end-diastolic volumes at rest, the changes in LV volume with head-up and head-down tilt testing to assess LV distensibility were similar to controls [11].

Residual effects from the pretransplant period (such as malnutrition and a deconditioned state), associated conditions (such as neuromuscular disease), and medication side effects (such as anemia and hypertension) may also affect exercise performance.

Exercise Testing in Pediatric Heart Transplant Recipients

Infant HT recipients may not undergo their first cardiopulmonary exercise test (CPET) until 6 or 8 years after transplant, whereas teenage HT recipients may be referred for CPET within the first year. Given this variability, it is important to be aware of both short- and long-term physiologic factors that may affect CPET results in HT recipients. The test objectives include assessment of functional capacity, exercise-induced arrhythmias, and blood pressure response. Some centers also perform stress echocardiography as a noninvasive alternative to coronary angiography to screen for coronary artery disease with imaging performed at rest and immediately postexercise [12].

Electrocardiography and Heart Rate Changes

The resting electrocardiogram (ECG) in pediatric HT recipients often has an incomplete right bundle branch block [4, 13]. In patients transplanted with the older surgical technique of biatrial anastomoses, dual P waves may be present with non-conducting P waves from the posterior atrial wall. Several findings on CPET—high resting heart rate, gradual rather than quick increase in heart rate at the beginning of exercise, subnormal peak heart rate (chronotropic impairment), and persistent tachycardia for several minutes after exercise (attenuated heart rate recovery)—can be explained by autonomic denervation. These findings improve with time (years) in recipients whose hearts have developed autonomic, usually sympathetic reinnervation (see Fig. 26.1) [14, 15].

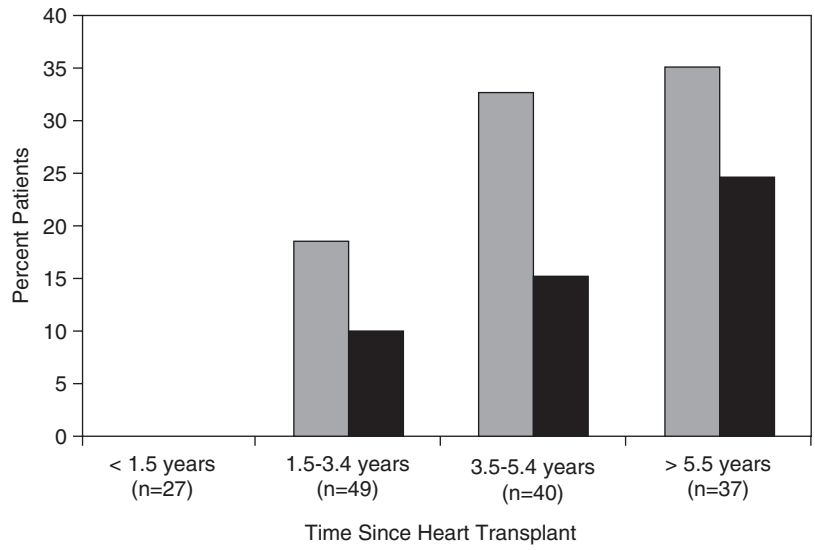


Fig. 26.1 Improvement in heart rate recovery over time in pediatric HT recipients. Percent of exercise tests in HT recipients with 1-minute HR recovery ≥10th percentile (gray bars) and ≥25th percentile (black bars) for age and gender with increasing time since transplant. These values were <10th percentile for all patients at <1.5 years after transplant. (Reprinted with permission from [14])

Oxygen Consumption During Exercise

Despite replacement with a normal heart, cardiac output with exercise (and therefore peak oxygen consumption ($\dot{V}_{O2}$)) does not normalize in pediatric HT recipients. Due to a common finding of chronotropic impairment and sometimes impaired stroke volume response, the peak $\dot{V}_{O2}$ achieved in patients early after HT is usually low [10, 16]. One series reported a peak $\dot{V}_{O2}$ of 59% ± 15% predicted during the first exercise test after transplant. In patients undergoing CPET within the first year after transplant, the average peak $\dot{V}_{O2}$ was even lower: only 50% predicted. After an initial improvement in peak $\dot{V}_{O2}$, thought to be secondary to improvements in nutritional status and graft function, there was a steady decline in peak $\dot{V}_{O2}$ over years. This decline correlated with echocardiographic markers of diastolic dysfunction but not with changes in systolic function or heart rate [17].

Other studies have demonstrated better exercise capacity in children who were transplanted at a younger age, particularly in infant recipients, in whom peak $\dot{V}_{O2}$ was low-normal (32.3 ± 5.6 ml/kg/min, 88% predicted) when first tested [18, 19]. These patients had better chronotropic response (84% predicted) compared to that reported in other series, suggesting a higher proportion of patients with sympathetic reinnervation.

Peak O_2 pulse, a surrogate for maximum stroke volume during exercise, is often low early after HT but improves to near-normal over time. In one study, O_2 pulse ranged from 50% to 70% of normal in patients who underwent exercise testing 1 month after transplant, likely due to factors associated with pretransplant deconditioning [16]. By contrast, O_2 pulse in infant HT recipients who underwent CPET several years after transplant was normal [14].

Ventilatory Response

Exercise testing performed in patients in chronic heart failure prior to transplant often demonstrates impaired ventilatory efficiency with increased physiologic dead space. This impairment in gas exchange is seen as an elevation in the ratio of minute ventilation ($\dot{V}_E$) and CO_2 production ($\dot{V}_{CO2}$). Adult studies demonstrate rapid improvement in the $\dot{V}_E/\dot{V}_{CO2}$ slope within 6 months after HT, with near normalization of values by 24 months [16]. An elevated $\dot{V}_E/\dot{V}_{CO2}$ slope on CPET in pediatric HT recipients may suggest the presence of high LV filling pressures and V/Q mismatch.

Prototypical Patient

The patient was a 15-year-old adolescent who had a familial dilated cardiomyopathy and underwent a HT 1 year prior to the CPET. Aside from an episode of mild acute rejection (detected on a routine, surveillance endomyocardial biopsy 2 weeks post-HT) that was treated successfully with a transient increase in her immunosuppressive therapy, she had been rejection-free and doing well. She did struggle with obesity issues related, at least in part, to her prednisone therapy. She also had hypertension (probably also due to her immunosuppressive regimen) and was maintained on anti-hypertensive (calcium channel blocker) therapy. She was not medicated with a beta-blocker. The CPET (Table 26.1 and Fig. 26.2) was performed as a component of her 1-year post-HT clinical assessment.

Table 26.1 Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	14.0
Peak $\dot{V}_{O2}$ (%predicted)	77
Peak work rate (W)	101
Peak work rate (%predicted)	94
Peak RER	1.17
Peak O2 pulse (%predicted)	117
Resting heart rate (bpm)	95
Peak heart rate (bpm)	126
Peak heart rate (%predicted)	66
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	60
$\dot{V}_E/\dot{V}_{CO2}$ slope	31
End-tidal pCO_2 at VAT (mm Hg)	38
End-tidal pCO_2 during exercise	normal
Forced vital capacity (%predicted)	93
FEV1 (%predicted)	87
FEF 25–75 (%predicted)	69
Stress echocardiography	normal

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

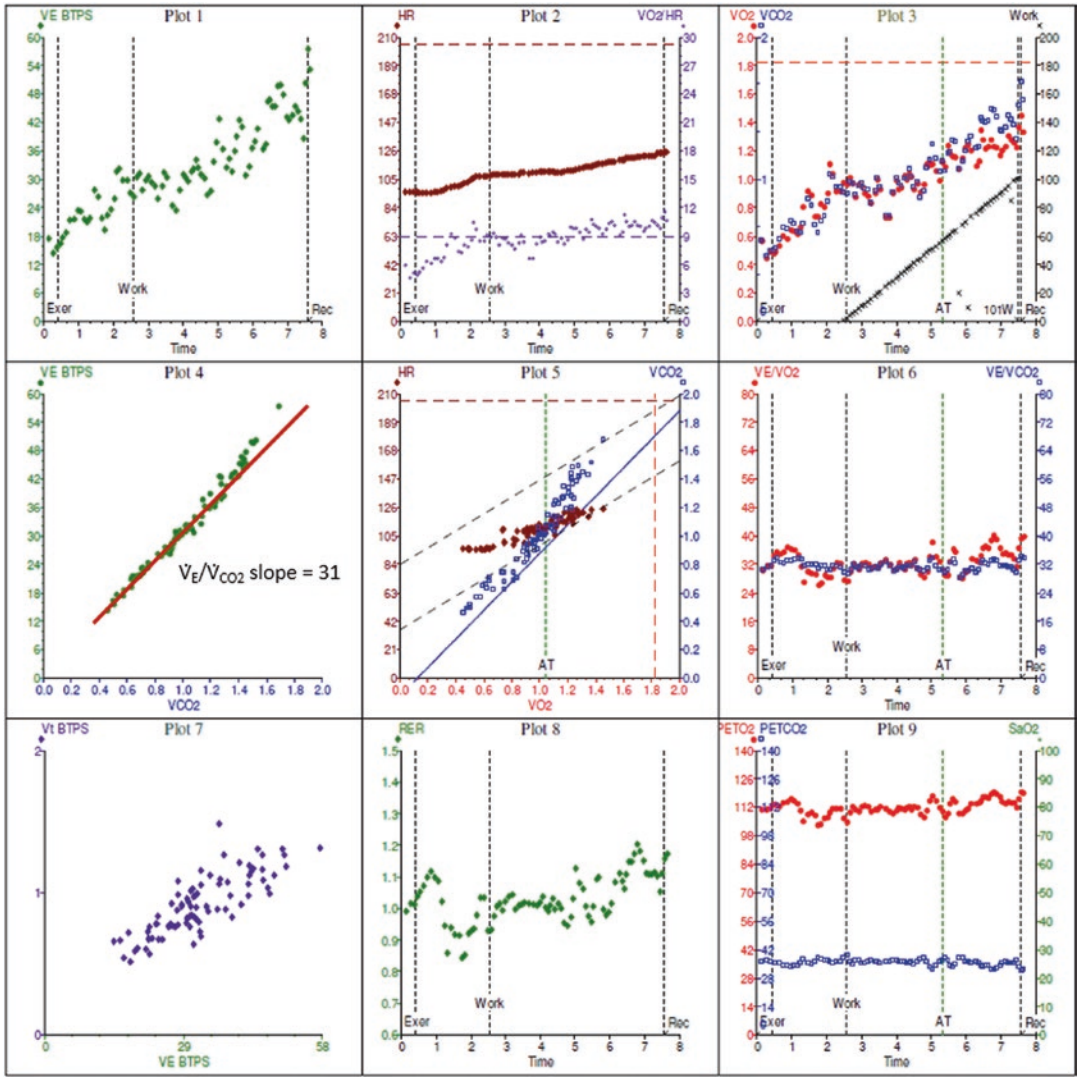


Fig. 26.2 9-panel graph from cardiopulmonary exercise test of prototypical pediatric patient who has had a heart transplant. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, $PETCO_2$ end-tidal pCO_2, $PETO_2$ end-tidal pO_2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, $\dot{V}_{O2}$ oxygen consumption, V_{O2}/HR oxygen pulse

Based upon her peak respiratory exchange ratio, she expended a good effort. Although her %predicted peak $\dot{V}_{O2}$ was mildly depressed, her peak work rate and $\dot{V}_{O2}$ at the VAT were normal. Her weight-normalized $\dot{V}_{O2}$ values, however, were disproportionately low, due to her obesity (body mass index 38.2). Her baseline heart rate was slightly elevated, and her heart rate increased slowly during exercise. Her peak heart rate was quite depressed. Her oxygen pulse at peak exercise, however, was 17% above the predicted normal value. Her tidal volume at peak exercise was slightly lower than expected. Her $\dot{V}_E/\dot{V}_{CO2}$ slope was mildly elevated and her end-tidal pCO_2 was in the low-normal range. A mild obstructive pattern was present on her baseline spirometry, but her breathing reserve was slightly high. No ectopy or significant STT changes were detected. Stress echocardiography was normal.

The patient's heart rate response to exercise (high resting heart rate, blunted heart rate increase during exercise, and low peak exercise heart rate) is typical of patients with denervated hearts following HT. The supra-normal oxygen pulse at peak exercise reflects the compensatory increase in stroke volume (based upon the Starling mechanism) that normally occurs in the presence of a chronotropic defect. The normal stress echocardiography supports this conjecture. The robust stroke volume response allows the patient to have a normal VAT and only mildly depressed peak $\dot{V}_{O2}$, despite the severe chronotropic dysfunction. The low tidal volume at peak exercise probably is a result of her obesity; generating a full excursion of her heavy chest wall is difficult and associated with unfavorable energetics. The mild obstructive pattern on her baseline spirometry is common in patients with obesity (and consistent with a past history of mild asthma). The ample breathing reserve at peak exercise suggests that the patient was not limited by respiratory factors.

Conclusion

CPET is a useful tool for assessing the functional status in pediatric HT recipients. The denervated heart has a unique physiology, often with resting tachycardia due to a lack of parasympathetic tone, as well as a reliance on circulating catecholamines to augment heart rate. These limitations affect exercise performance adversely. Over time, exercise performance may improve in patients with autonomic reinnervation or deteriorate in those with worse graft function. Serial assessment has a potential utility in monitoring cardiovascular health of pediatric HT recipients.

References

1. Rossano JW, Cherikh WS, Chambers DC, Goldfarb S, Khush K, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: twentieth pediatric heart transplantation report-2017; focus theme: allograft ischemic time. J Heart Lung Transplant. 2017;36(10):1060–9.
2. Patel JN, Kavey RE, Pophal SG, Trapp EE, Jellen G, Pahl E. Improved exercise performance in pediatric heart transplant recipients after home exercise training. Pediatr Transplant. 2008;12(3):336–40.
3. Uzark K, Griffin L, Rodriguez R, Zamberlan M, Murphy P, Nasman C, et al. Quality of life in pediatric heart transplant recipients: a comparison with children with and without heart disease. J Heart Lung Transplant. 2012;31(6):571–8.
4. Allen HDSR, Penny DJ, Cetta F, Feltes TF. Moss and adams heart disease in infants, children, and adolescents: including the fetus and young adult. 9th ed. Philadelphia: Wolters Kluwer; 2016.
5. Awad M, Czer LS, Hou M, Golshani SS, Goltche M, De Robertis M, et al. Early denervation and later reinnervation of the heart following cardiac transplantation: a review. J Am Heart Assoc. 2016;5(11):e004070.
6. Di Carli MF, Tobes MC, Mangner T, Levine AB, Muzik O, Chakroborty P, et al. Effects of cardiac sympathetic innervation on coronary blood flow. N Engl J Med. 1997;336(17):1208–16.
7. Bengel FM, Ueberfuhr P, Schiepel N, Nekolla SG, Reichart B, Schwaiger M. Effect of sympathetic reinnervation on cardiac performance after heart transplantation. N Engl J Med. 2001;345(10):731–8.
8. Lunze FI, Colan SD, Gauvreau K, Chen MH, Perez-Atayde AR, Blume ED, et al. Cardiac allograft function during the first year after transplantation in rejection-free children and young adults. Circ Cardiovasc Imaging. 2012;5(6):756–64.
9. Pahl E, Miller SA, Griffith BP, Fricker FJ. Occult restrictive hemodynamics after pediatric heart transplantation. J Heart Lung Transplant. 1995;14(6 Pt 1):1109–15.
10. Peterson S, Su JA, Szmuszkovicz JR, Johnson R, Sargent B. Exercise capacity following pediatric heart transplantation: a systematic review. Pediatr Transplant. 2017;21(5):e12922.
11. Altamirano-Diaz LA, Nelson MD, West LJ, Khoo NS, Rebeyka IM, Haykowsky MJ. Left ventricular distensibility does not explain impaired exercise capacity in pediatric heart transplant recipients. J Heart Lung Transplant. 2013;32(1):63–9.
12. Chen MH, Abernathey E, Lunze F, Colan SD, O'Neill S, Bergersen L, et al. Utility of exercise stress echocardiography in pediatric cardiac transplant recipients: a single-center experience. J Heart Lung Transplant. 2012;31(5):517–23.
13. Thajudeen A, Stecker EC, Shehata M, Patel J, Wang X, McAnulty JH Jr, et al. Arrhythmias after heart transplantation: mechanisms and management. J Am Heart Assoc. 2012;1(2):e001461.
14. Singh TP, Gauvreau K, Rhodes J, Blume ED. Longitudinal changes in heart rate recovery after maximal exercise in pediatric heart transplant recipients: evidence of autonomic re-innervation? J Heart Lung Transplant. 2007;26(12):1306–12.
15. Giardini A, Fenton M, Derrick G, Burch M. Impairment of heart rate recovery after peak

exercise predicts poor outcome after pediatric heart transplantation. Circulation. 2013;128(11 Suppl 1):S199–204.
16. Chiu HH, Wu MH, Wang SS, Lan C, Chou NK, Chen SY, et al. Cardiorespiratory function of pediatric heart transplant recipients in the early postoperative period. Am J Phys Med Rehabil. 2012;91(2):156–61.
17. Davis JA, McBride MG, Chrisant MR, Patil SM, Hanna BD, Paridon SM. Longitudinal assessment of cardiovascular exercise performance after pediatric heart transplantation. J Heart Lung Transplant. 2006;25(6):626–33.
18. Abarbanell G, Mulla N, Chinnock R, Larsen R. Exercise assessment in infants after cardiac transplantation. J Heart Lung Transplant. 2004;23(12):1334–8.
19. Dipchand AI, Manlhiot C, Russell JL, Gurofsky R, Kantor PF, McCrindle BW. Exercise capacity improves with time in pediatric heart transplant recipients. J Heart Lung Transplant. 2009;28(6):585–90.

27 Cardiac Rehabilitation and Exercise Training

Ana Ubeda-Tikkanen and Naomi S. Gauthier

Cardiac rehabilitation programs for adults with acquired heart disease have been studied extensively. In addition to improving peak $\dot{V}_{O2}$ and exercise capacity, they have been found to reduce morbidity and mortality, improve quality of life, and reduce economic costs [1–4]. They also have a salutary effect upon standard cardiovascular risk factors such as lipid profiles, adiposity, and hypertension [4–8]. Furthermore, the importance of physical fitness has been emphasized by studies in adults that have concluded that being unfit is associated with a relative risk for cardiovascular death that exceeds the risks associated with smoking, elevated systolic blood pressure, hypercholesterolemia, or obesity [5, 8].

A. Ubeda-Tikkanen
Physical Medicine and Rehabilitation, Department of Pediatric Rehabilitation, Boston Children's Hospital, Boston, MA, USA

Physical Medicine and Rehabilitation, Department of Pediatric Rehabilitation, Spaulding Rehabilitation Hospital, Boston, MA, USA

Physical Medicine and Rehabilitation, Department of Pediatric Rehabilitation, Harvard Medical School, Boston, MA, USA

N. S. Gauthier (✉)
Cardiac Fitness Program, Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: naomi.gauthier@cardio.chboston.org

One might expect that the benefits associated with cardiac rehabilitation in adults with acquired cardiovascular disease would also be recognized among children and adults with congenital heart disease (CHD). However, relatively few, comparatively small clinical studies have been conducted in these populations. Several small studies have evaluated the short-term benefits of exercise training programs in children with congenital heart disease. Although results have varied, improvements in peak $\dot{V}_{O2}$ are usually encountered, and sometimes exceed 20% [9–25]. Most of the improvement appears to be attributable to an increase in the oxygen pulse at peak exercise, a phenomenon that can only be explained by a training-induced increased stroke volume and/or oxygen extraction at peak exercise [11, 16]. In one study, the short-term improvements were sustained 6–9 months after the termination of the rehabilitation program (1 year after the pre-rehabilitation study) and were also 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, composed of 18 children with similar diagnoses, observed over the same time period [12].

The benefits associated with exercise training in children with CHD (and adults with acquired heart disease) should also extend to adults with CHD. However, few studies have been undertaken to support this conjecture. One study of 17 adults

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_27

with tetralogy of Fallot (of whom 9 participated in a home/hospital-based exercise program for 12 weeks, and 8 continued to pursue their habitual daily activities) reported a small (7.8%) but statistically significant increase in peak $\dot{V}_{O2}$ in the exercise group but not in the control subjects [26]. In another study, the exercise duration of a group of 61 adult patients with a variety of CHD diagnoses improved after a 10-week home-based exercise program [27]. Similar beneficial effects were detected in another study of 11 patients [28]. More recently, a randomized trial of cardiac rehabilitation in 28 adults with CHD (13 cardiac rehabilitation and 15 standard of care) reported that rehabilitation was associated with statistically significant improvements in peak $\dot{V}_{O2}$ and symptomatology [29].

As noted in previous chapters, aerobic fitness (peak $\dot{V}_{O2}$) has been found to be a strong predictor of survival in a variety of CHDs and other cardiovascular disorders. It is therefore tempting to speculate that a rehabilitation-induced improvement in peak $\dot{V}_{O2}$ would translate into a survival benefit for patients with these conditions. However, this conjecture has not yet been subjected to rigorous clinical study.

Cardiac rehabilitation for children and young adults with CHD appears to be a very low-risk undertaking. A serious adverse event has not been reported by any of the studies of cardiac rehabilitation in these populations [8, 25]. Indeed, even among selected patients with serious conditions, such as pulmonary hypertension, exercise training appears to be a low risk and beneficial undertaking [30–35].

In the adult acquired heart disease population, only ~14–35% of potential candidates for exercise training/cardiac rehabilitation actually receive this therapy [8]. Among children, adolescents, and young adults with CHD, this percentage is undoubtedly much lower. This is extremely unfortunate because, as detailed in previous chapters, the exercise function of patients with CHD is often decreased compared to normal subjects, even after "reparative" surgery. Although some of this exercise dysfunction is without doubt related to residual hemodynamic defects, inactivity and deconditioning (often because of restrictions inappropriately imposed by family members, teachers, coaches, or the patients themselves) undoubtedly also contribute to this problem [36, 37]. This component of their disability should theoretically respond favorably to exercise training programs.

Beyond the beneficial effects enumerated above, physical activity can also provide a multitude of other health, cognitive, social, and emotional benefits to children with CHD. These benefits are far reaching and should be considered when evaluating the desirability, success, and effectiveness of a pediatric cardiac rehabilitation program, especially in light of the neurodevelopmental issues commonly encountered in this population. Overall health benefits of exercise in children include a decrease in obesity, cholesterol reduction, and improvements in immune function [38]. Regular exercise also has a significant beneficial impact upon cognition, focus, memory, and attention. Physical activity has also been found to result in improved school performance, standardized test scores, school attendance, memory, and attention [39–44]. Indeed, exercise has been recognized as an effective adjunct in the treatment of attention-deficit hyperactivity disorder, depression, and anxiety [45–47]. Anxiety is a major comorbidity in patients with CHD (and their families); the potential value of exercise programs in the management of this often debilitating condition is therefore intriguing.

Playing with other children is a rite of childhood that is important for social and emotional development. Moreover, lack of participation in and physical activities has been associated with an increased likelihood of negative behaviors such as smoking, substance abuse, increased screen time, and failure to wear a seatbelt [48]. Hence it is particularly unfortunate (but all too common) for children with CHD to be unnecessarily restricted from physical activity. Exercise training/cardiac rehabilitation programs can help address this under-appreciated problem.

Components of Cardiac Rehabilitation Programs

According to the U.S. Centers for Medicaid and Medicare, cardiac rehabilitation for coronary artery disease patients includes physician-

prescribed exercise, cardiac risk factor modification, psychosocial assessment, and outcomes assessment. Specific core competencies are defined for each element. In addition, an Individualized Treatment Plan designed to meet each patient's specific needs, set goals, and track progress is mandated and should be signed by the supervising physician every 30 days. In addition to aerobic function, rehabilitation programs can and should address issues related to strength, weight, nutrition, and lifestyle [49].

Many of the components of an adult rehabilitation program may be applied to rehabilitation programs for patients with pediatric and adult CHD. Others require modification. For instance, at Boston Children's Hospital we have modified the adult coronary artery disease "risk factor modification" component into a format that better addresses the issues encountered in the pediatric and adult CHD population (Table 27.1).

Appropriate outcome metrics for each domain of a rehabilitation program for patients with CHD are yet to be defined, but will surely emerge as experience with pediatric cardiac rehabilitation evolves. Of course, differences in terms of age, time from surgery, functional impairments, and comorbidities found in this patient population compared to adults with acquired heart disease might mandate changes to the structure and/or components of cardiac rehabilitation programs [50].

Table 27.1 Proposal for mapping risk factor modification in coronary artery disease to congenital heart disease

CMS guidelines Other CV risk factors (coronary artery disease)	Proposed equivalencies Other CV risk factors (congenital heart disease)
BP management	Lipid/BP assessment
Lipid management	Neurocognitive/ developmental (readiness to learn)
Diabetes management	Other comorbidities
Tobacco cessation	Tobacco education

CMS US Centers for Medicare and Medicaid Services, *CV* cardiovascular, *BP* blood pressure

Barriers to Success

Healthcare System Barriers: Referral of Appropriate Patients

Although adult cardiac rehabilitation programs designed to address patients with coronary artery disease have been shown to decrease mortality and provide significant health benefits for eligible patients, the programs are vastly underutilized in the United States [51]. Despite attempts to design systems to address low enrollment rates, it has been estimated that only 20% of eligible patients are referred to rehabilitation programs [49]. In the CHD community, consistent definitions of eligibility criteria have not been drafted or adopted widely, and the number of patients eligible for rehabilitation is not known. It is clear, however, that cardiac rehabilitation is vastly underutilized in the pediatric and CHD population. Hence, on a national scale, the first health system barrier that the pediatric cardiology community may need to address is defining patient eligibility. The second may be to design and implement measures (analogous to those undertaken by the adult cardiology community) to encourage providers to track program referrals and patient outcomes.

Patient- and Community-Related Factors

Adult cardiac rehabilitation programs confront a number of patient/community-related barriers that include issues relating to availability of programs, transportation, hours of operation, cost of care, knowledge and perceptions, health disparities, availability of appropriately trained staff, and awareness of existing programs by healthcare teams or families [51]. Similar issues, usually magnified by the more limited availability of rehabilitation programs appropriate for children and young adults, are encountered by pediatric rehabilitation programs [52–54]. All of these are potentially modifiable if there is collective will and a groundswell within the field to overcome these factors.

Boston Children's Hospital Experience

At Boston Children's Hospital we began formal recruitment of patients to our outpatient Cardiac Fitness Program in September 2016. In the absence of start-up funds, we initially relied primarily upon existing physical and human resources available through our exercise laboratories. (Financial analyses revealed that a free-standing program could not be profitable, and it was therefore necessary to begin with this less ambitious approach.) Our definition of eligibility included patients with congenital or pediatric acquired heart disease ages 8 years and older who were debilitated, sedentary, recovering from surgery, or required guidance and education in safe and effective exercise practices. We excluded the highest risk patients, such as those with significant hypertrophic cardiomyopathy, high level tachyarrhythmias, or uncontrolled severe pulmonary hypertension. We were constrained by limited space and capacity and therefore limited our catchment to internal cardiology faculty. We have found that of the patients referred, about half have actually started and stayed with the program; others were unreachable, chose not to participate after the initial contact, or dropped out (Fig. 27.1). Insurance coverage has rarely been a barrier (4/63), but limited transportation resources and a limited availability of safe places for exercise outside of the program have been commonly encountered issues.

All patients referred to the program have an initial visit with a dedicated cardiologist to review their eligibility, assess goals and, together with the training staff, formulate an individual treatment plan. Prior to initiating the program, patients undergo a cardiopulmonary exercise test (CPET) for baseline data and to determine that exercise is safe for the patient. In addition, baseline measurements of strength and flexibility are undertaken and questionnaires exploring the patient's mindset are also administered. The training program is conducted in the exercise physiology laboratory and includes aerobic exercise (stationary cycle and/or treadmill), strength and balance training (light weights, floor exercises, yoga, etc.), and activity and dietary counseling. Twice weekly one-hour sessions are conducted under the supervision of a trained exercise physiologist. Telemetry is employed for the initial (and, if necessary, subsequent) sessions. Safety equipment (a code cart, oxygen, suction, etc.) and a cardiologist are always present within or in the vicinity of the laboratory. Depending upon patient needs and insur-

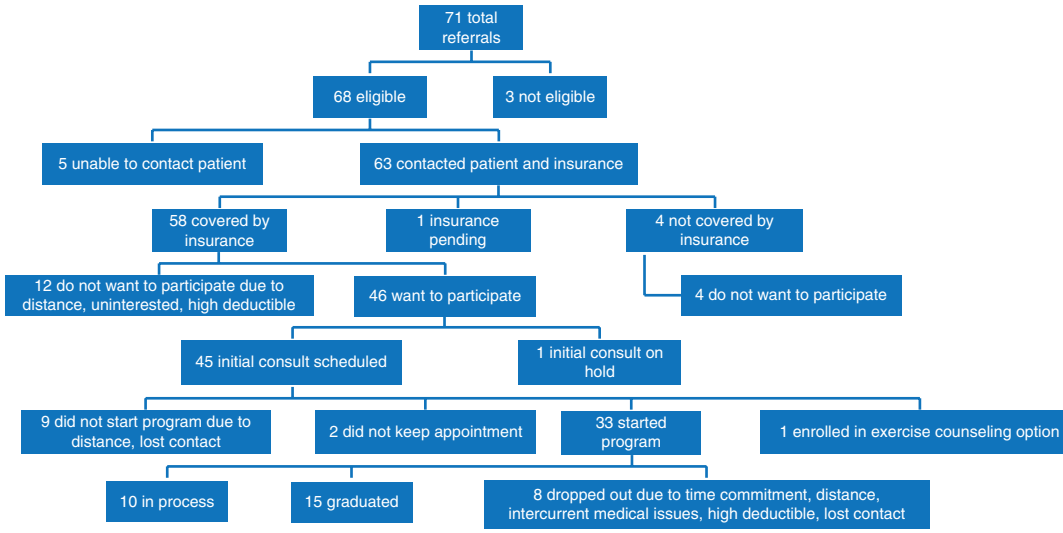


Fig. 27.1 Flow chart of patients who have been referred for cardiac rehabilitation at Boston Children's Hospital

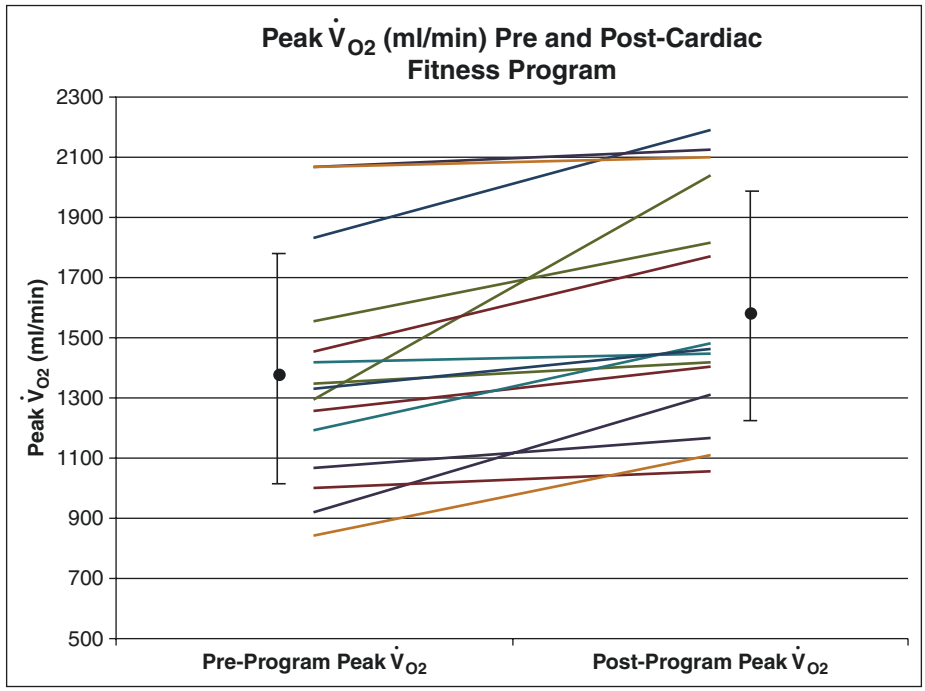


Fig. 27.2 Impact of cardiac fitness program on peak $\dot{V}O_2$. Each line represents an individual patient. The average increase was almost 18%

ance coverage, the program typically extends for 24–36 sessions. The training program is supplemented with personalized home exercise routines that are supported by an online application.

For our first 15 graduates, 12 have had a >5% improvement in their peak $\dot{V}_{O2}$ and 8 have had a >10% increase (Fig. 27.2). Improvements in their strength and flexibility have also been commonly observed. Preliminary data regarding our program's impact upon mindset and behavior have also been encouraging. With these lessons in mind, our program now consists of:

1. In-person fitness training sessions.
2. A mindset journal with guided exercises based in positive psychology and sports psychology
3. An interactive application for smart phones or computers that is both a motivator to help patients exercise effectively between sessions and a data collection tool for later study
4. Custom-designed home exercise videos featuring patients and professional athletes that provide instruction for how to exercise independently, as well as add to a sense of fun, excitement, and unity among the participants
5. Nutrition counseling

The responses from patients, families, referring physicians, and administrators have been encouraging, and have helped us to acquire grants (that have allowed us to develop some of the features described) and other support that will permit us to expand our program and acquire dedicated space within the hospital and other facilities. Testimonials from the patients and parents and the anecdotal interest from centers around the United States have inspired us and we anticipate considerable progress as a field going forward.

Cardiac Rehabilitation Experience in Madrid

The pediatric cardiac rehabilitation program started in the Gregorio Marañon Hospital as a collaboration between the pediatric cardiology and rehabilitation departments in November 2010. The initial inclusion criteria included Fontan patients who were ε 6 years old, able to perform a CPET, with %predicted peak $\dot{V}_{O2}$ ≤80% and had no concerning findings (fall in blood pressure, serious arrhythmia, etc.) on the CPET. The CPET was also used to help create individualized treatment programs.

Since its initiation, the program's inclusion criteria have been extended to other diagnoses. Prior to participating in the program, patients are cleared by their primary cardiologist. A strength assessment is also performed and a quality of life questionnaire is completed pre- and post-program.

The staff is composed of a pediatric physical therapist and a pediatric physiatrist. In case of emergency, a pediatric cardiologist is always present within the facility. The program is conducted in the pediatric rehabilitation therapeutic gym. Patients are monitored with telemetry for the first 6 sessions, and as needed thereafter. Vital signs are recorded at the beginning and end of each session.

The program lasts for 12 weeks, with 1-hour sessions twice a week. Each session consists of a warm up, respiratory muscle training, child-friendly aerobic training (obstacle races, circuits, treadmill, bike, and Wii Fit), low-resistance training, and cool down. Patients are encouraged to engage in additional physical activity at home twice a week. Activity logs are provided. Targeted heart rate during aerobic exercise is at or above the heart rate at the anaerobic threshold on CPET. Patients are also trained to use the Borg rate of perceived exertion scale. At the end of the program, patients are encouraged to continue to participate in structured physical activity at least twice a week.

While the children are in their rehabilitation sessions, their parents participate in educational sessions once a week. Subjects include: cardiac diagnoses and pathophysiology, physical activity and CHD, cardiac medications, nutrition, and comorbidities (neurodevelopment, learning and behavioral issues, feeding, motor, and problems with activities of daily living).

Of the first 37 patients who participated, there were 24 Fontan patients, 3 with repaired tetralogy of Fallot, 3 who had undergone heart transplantation, 3 who had aortic valvuloplasties, 1 with repaired total anomalous pulmonary venous return, 1 with repaired double outlet right ventricle and pulmonary hypertension, 1 with repaired transposition of the great arteries with pulmonary hypertension, and with repaired transposition of the great arteries complicated by a myocardial infarction. Of these patients, 2 had severe pulmonary hypertension that required prostacyclin pumps. The patients' ages ranged from 6 to 17 years of age. Adherence to the program was high, with 85% coming to ε 80% of the training sessions. No serious adverse events occurred. Of the 35 patients with complete follow-up data, 25 had improved exercise function (details awaiting publication).

References

1. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Am Heart J. 2011;162(4):571–584 e572.
2. Leon AS, Franklin BA, Costa F, Balady GJ, Berra KA, Stewart KJ, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association Scientific Statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation. 2005;111(3):369–76.
3. Piepoli MF, Conraads V, Corra U, Dickstein K, Francis DP, Jaarsma T, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Heart Fail. 2011;13(4):347–57.
4. Green DJ, O'Driscoll G, Joyner MJ, Cable NT. Exercise and cardiovascular risk reduction: time to update the rationale for exercise? J Appl Physiol (1985). 2008;105(2):766–8.

5. Thijssen DH, Maiorana AJ, O'Driscoll G, Cable NT, Hopman MT, Green DJ. Impact of inactivity and exercise on the vasculature in humans. Eur J Appl Physiol. 2010;108(5):845–75.
6. Shephard RJ, Balady GJ. Exercise as cardiovascular therapy. Circulation. 1999;99(7):963–72.
7. Dimmeler S, Zeiher AM. Exercise and cardiovascular health: get active to "aktivate" your endothelial nitric oxide synthase. Circulation. 2003;107(25):3118–20.
8. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873–934.
9. Balfour IC, Drimmer AM, Nouri S, Pennington DG, Hemkens CL, Harvey LL. Pediatric cardiac rehabilitation. Am J Dis Child. 1991;145(6):627–30.
10. Longmuir PE, Turner JA, Rowe RD, Olley PM. Postoperative exercise rehabilitation benefits children with congenital heart disease. Clin Invest Med. 1985;8(3):232–8.
11. Rhodes J, Curran TJ, Camil L, Rabideau NC, Fulton DR, Gauthier NS, et al. Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. Pediatrics. 2005;116:1339–45.
12. Rhodes J, Curran TJ, Camil L, Rabideau NC, Fulton DR, Gauthier NS, et al. Sustained effects of cardiac rehabilitation in children with serious congenital heart disease. Pediatrics. 2006;118:e586–93.
13. Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.
14. Takken T, Bongers BC, van Brussel M, Haapala EA, Hulzebos EHJ. Cardiopulmonary exercise testing in pediatrics. Ann Am Thorac Soc. 2017;14(Supplement_1):S123–8.
15. Washington RL. Cardiac rehabilitation programmes in children. Sports Med. 1992;14(3):164–70.
16. Opocher F, Varnier M, Sanders SP, Tosoni A, Zaccaria M, Stellin G, et al. Effects of aerobic exercise training in children after the Fontan operation. Am J Cardiol. 2005;95:150–2.
17. Bradley LM, Galioto FM Jr, Vaccaro P, Hansen DA, Vaccaro J. Effect of intense aerobic training on exercise performance in children after surgical repair of tetralogy of fallot or complete transposition of the great arteries. Am J Cardiol. 1985;56(12):816–8.
18. Cordina RL, O'Meagher S, Karmali A, Rae CL, Liess C, Kemp GJ, et al. Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in Fontan physiology. Int J Cardiol. 2013;168(2):780–8.
19. Fredriksen PM, Kahrs N, Blaasvaer S, Sigurdsen E, Gundersen O, Roeksund O, et al. Effect of physical training in children and adolescents with congenital heart disease. Cardiol Young. 2000;10:107–14.
20. Goldberg B, Fripp RR, Lister G, Loke J, Nicholas JA, Talner NS. Effect of physical training on exercise performance of children following surgical repair of congenital heart disease. Pediatrics. 1981;68(5):691–9.
21. Ruttenberg HD, Adams TD, Orsmond GS, Conlee RK, Fisher AG. Effects of exercise training on aerobic fitness in children after open heart surgery. Pediatr Cardiol. 1983;4(1):19–24.
22. Sutherland N, Jones B, d'Udekem Y. Should we recommend exercise after the Fontan procedure? Heart Lung Circ. 2015;24(8):753–68.
23. Minamisawa S, Nakazawa M, Momma K, Imai Y, Satomi G. Effect of aerobic training on exercise performance in patients after the Fontan operation. Am J Cardiol. 2001;88(6):695–8.
24. Moalla W, Maingourd Y, Gauthier R, Cahalin LP, Tabka Z, Ahmaidi S. Effect of exercise training on respiratory muscle oxygenation in children with congenital heart disease. Eur J Cardiovasc Prev Rehabil. 2006;13(4):604–11.
25. Tikkanen AU, Oyaga AR, Riano OA, Alvaro EM, Rhodes J. Paediatric cardiac rehabilitation in congenital heart disease: a systematic review. Cardiol Young. 2012;22(3):241–50.
26. Therrien J, Fredriksen P, Walker M, Granton J, Reid GJ, Webb G. A pilot study of exercise training in adult patients with repaired tetralogy of fallot. Can J Cardiol. 2003;19(6):685–9.
27. Dua JS, Cooper AR, Fox KR, Graham SA. Physical activity levels in adults with congenital heart disease. Eur J Cardiovasc Prev Rehabil. 2007;14(2):287–93.
28. Holloway TM, Chesssex C, Grace SL, Oechslin E, Spriet LL, Kovacs AH. A call for adult congenital heart disease patient participation in cardiac rehabilitation. Int J Cardiol. 2011;150(3):345–6.
29. Opotowsky AR, Rhodes J, Landzberg MJ, Bhatt AB, Shafer KM, Yeh DD, et al. A randomized trial comparing cardiac rehabilitation to standard of care for adults with congenital heart disease. World J Pediatr Congenit Heart Surg. 2018;9(2):185–93.
30. Chan L, Chin LMK, Kennedy M, Woolstenhulme JG, Nathan SD, Weinstein AA, et al. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. Chest. 2013;143(2):333–43.
31. Fox BD, Kassirer M, Weiss I, Raviv Y, Peled N, Shitrit D, et al. Ambulatory rehabilitation improves exercise capacity in patients with pulmonary hypertension. J Card Fail. 2011;17(3):196–200.
32. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation. 2006;114(14):1482–9.
33. Grunig E, Ehlken N, Ghofrani A, Staehler G, Meyer FJ, Juenger J, et al. Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. Respiration. 2011;81(5):394–401.
34. Arena R, Lavie CJ, Borghi-Silva A, Daugherty J, Bond S, Phillips SA, et al. Exercise training in group 2 pulmonary hypertension: which intensity and what modality. Prog Cardiovasc Dis. 2016;59(1):87–94.

35. Becker-Grunig T, Klose H, Ehlken N, Lichtblau M, Nagel C, Fischer C, et al. Efficacy of exercise training in pulmonary arterial hypertension associated with congenital heart disease. Int J Cardiol. 2013;168(1):375–81.
36. Falk B, Bar-Mor G, Zigel L, Yaaron M, Beniamini Y, Zeevi B. Daily physical activity and perception of condition severity among male and female adolescents with congenital heart disease. J Pediatr Nurs. 2006;21(3):244–9.
37. McCrindle BW, Williams RV, Mital S, Clark BJ, Russell JL, Klein G, et al. Physical activity levels in children and adolescents are reduced after the Fontan procedure, independent of exercise capacity, and are associated with lower perceived general health. Arch Dis Child. 2007;92(6):509–14.
38. Sothern MS, Loftin M, Suskind RM, Udall JN, Blecker U. The health benefits of physical activity in children and adolescents: implications for chronic disease prevention. Eur J Pediatr. 1999;158(4):271–4.
39. Watson A, Timperio A, Brown H, Best K, Hesketh KD. Effect of classroom-based physical activity interventions on academic and physical activity outcomes: a systematic review and meta-analysis. Int J Behav Nutr Phys Act. 2017;14(1):114.
40. Alvarez-Bueno C, Pesce C, Cavero-Redondo I, Sanchez-Lopez M, Garrido-Miguel M, Martinez-Vizcaino V. Academic achievement and physical activity: a meta-analysis. Pediatrics. 2017;140(6):e20171498.
41. Donnelly JE, Hillman CH, Castelli D, Etnier JL, Lee S, Tomporowski P, et al. Physical activity, fitness, cognitive function, and academic achievement in children: a systematic review. Med Sci Sports Exerc. 2016;48(6):1197–222.
42. Wright CM, Duquesnay PJ, Anzman-Frasca S, Chomitz VR, Chui K, Economos CD, et al. Study protocol: the Fueling Learning through Exercise (FLEX) study – a randomized controlled trial of the impact of school-based physical activity programs on children's physical activity, cognitive function, and academic achievement. BMC Public Health. 2016;16(1):1078.
43. Chaddock-Heyman L, Erickson KI, Holtrop JL, Voss MW, Pontifex MB, Raine LB, et al. Aerobic fitness is associated with greater white matter integrity in children. Front Hum Neurosci. 2014;8:584.
44. Kao SC, Westfall DR, Parks AC, Pontifex MB, Hillman CH. Muscular and aerobic fitness, working memory, and academic achievement in children. Med Sci Sports Exerc. 2017;49(3):500–8.
45. Pontifex MB, Saliba BJ, Raine LB, Picchietti DL, Hillman CH. Exercise improves behavioral, neurocognitive, and scholastic performance in children with attention-deficit/hyperactivity disorder. J Pediatr. 2013;162(3):543–51.
46. Blumenthal JA, Smith PJ, Hoffman BM. Is exercise a viable treatment for depression? ACSMs Health Fit J. 2012;16(4):14–21.
47. Carek PJ, Laibstain SE, Carek SM. Exercise for the treatment of depression and anxiety. Int J Psychiatry Med. 2011;41(1):15–28.
48. Pate RR, Heath GW, Dowda M, Trost SG. Associations between physical activity and other health behaviors in a representative sample of us adolescents. Am J Public Health. 1996;86(11):1577–81.
49. Anonymous. Guidelines for cardiac rehabilitation and secondary prevention programs. 5th ed. Champaign: Human Kinetics; 2013.
50. Ubeda Tikkanen A, Nathan M, Sleeper LA, Flavin M, Lewis A, Nimec D, et al. Predictors of postoperative rehabilitation therapy following congenital heart surgery. J Am Heart Assoc. 2018;7(10):e008094.
51. Balady GJ, Ades PA, Bittner VA, Franklin BA, Gordon NF, Thomas RJ, et al. Referral, enrollment, and delivery of cardiac rehabilitation/secondary prevention programs at clinical centers and beyond: a presidential advisory from the American Heart Association. Circulation. 2011;124(25):2951–60.
52. Murphy NA, Carbone PS. Promoting the participation of children with disabilities in sports, recreation, and physical activities. Pediatrics. 2008;121(5):1057–61.
53. Shields N, Synnot A. Perceived barriers and facilitators to participation in physical activity for children with disability: a qualitative study. BMC Pediatr. 2016;16:9.
54. Carver A, Timperio A, Crawford D. Playing it safe: the influence of neighbourhood safety on children's physical activity. A review. Health Place. 2008;14(2):217–27.

Summary of Lesions

28

Jonathan Rhodes

A diverse group of patients with congenital heart disease and other cardiovascular disorders may be referred for exercise testing in a pediatric exercise physiology laboratory. Within each diagnostic category, a wide spectrum of exercise function and physiologic abnormalities may be encountered. Although the results of cardiopulmonary exercise testing (CPET) are not diagnostic of any particular disorder, a number of patterns characteristic of the various congenital and other cardiovascular disorders can be identified. The picture that emerges from this intellectual exercise (which could only be imperfectly conveyed by this and the preceding chapters) is an awe-inspiring mosaic. It reflects the magnitude of the challenges and disabilities that patients with these diseases must confront and some of the physiologic adaptations that these challenges may engender (Table 28.1) [1]. An understanding of these patterns is invaluable to clinicians who care for these patients. Moreover, this knowledge, in conjunction with data from an individual's CPET, can also provide clinicians with a better appreciation of where, within the spectrum of physiologic dysfunction associated with a particular lesion, a patient's exercise function may fall. Undoubtedly, these insights can also be of great value to those who undertake to care for these complex patients.

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_28

Table 28.1 Characteristic abnormalities encountered in patients congenital and other pediatric cardiovascular disorders [1]

Defect	↓Peak $\dot{V}_{O2}$	↓Peak HR	↓O_2 pulse	↑ $\dot{V}_E/\dot{V}_{CO2}$	↓VAT	↓$P_{ET}CO_2$
Repaired TOF/truncus	+++	++	+++	+++	++	+++
Isolated PR	+	+	+	+	+	+
Fontan	++++	+++	++++	++++	+++	++++
Aortic valve disease	++	+	++	+	++	+
Coarctation	++	+	++	+	+++	+
S/P atrial switch	++++	++	++++	++	++	++
S/P arterial switch	+	+	+	++	+	++
Ebstein's anomaly	+++	++	+++	++	++	++
PVOD	++++	+	++++	++++	++++	++++
DCM	++++	+	++++	+++	++++	++
HCM	++	+	++	++	++	+
Mitochondrial disorder	++++	+	++++	+	++++	+
Glycogen storage disease	++++	+	++++	+	NA	+
Heart transplant	+++	++++	++	++	+++	++
Cyanotic CHD	++++	++	++++	++++	++++	++++

Legend: +: rarely present; ++: sometimes present; +++: often present; ++++: usually present
Cyanotic CHD unrepaired cyanotic congenital heart disease; *DCM* dilated cardiomyopathy; *HCM* hypertrophic cardiomyopathy; *NA* not applicable; *O_2 Pulse* oxygen pulse at peak exercise; *Peak HR* heart rate at peak exercise; *Peak $\dot{V}_{O2}$* oxygen consumption at peak exercise; *$P_{ET}CO_2$* end-tidal pCO2; *PR* pulmonary regurgitation, post valvuloplasty; *PVOD* pulmonary vascular obstructive disease; *TOF* tetralogy of Fallot; *Truncus* truncus arteriosus; *VAT* ventilatory anaerobic threshold; *V_E/V_{CO2}* slope of the linear portion of minute ventilation vs. carbon dioxide production curve

Reference

1. Rhodes J, Ubeda TA, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122(19):1957–67.

Part V

Electrophysiologic Issues

Syncope, Orthostatic Intolerance, and Exertional Symptoms

29

Mark E. Alexander

The vast majority of patients with syncope are appropriately managed with a careful history, physical, and electrocardiogram (EKG). This permits accurate identification of a well-characterized syndrome of typical, low-severity neurally mediated syncope [1]. In this setting, exercise testing is superfluous and adds cost and burden to patients.

Life-threatening causes of syncope can be recognized promptly. They have a familiar pattern of abrupt onset, atypical triggers (peak exertion, supine, as examples) with abnormal EKGs and echocardiograms permitting presumptive diagnoses in the vast majority of children [2]. For those children, exercise testing may be obtained as part of overall disease management.

Exercise testing has a critical role in the evaluation of those with potential cardiac syncope (with mid-exertional syncope the archetype of that presentation) and, in our practice, an increasing role in those with problematic symptoms. The advantages of exercise testing include the ability to screen for several different physiology responses at once, combined with rapid access to results. Head-up tilt testing has fallen out of favor in many pediatric groups [3]. Head-up tilt testing has a high incidence of physiologic positives [4] (as well has false negatives) and offers no ability to assess for latent arrhythmias.

Typical low-severity syncope is well recognized by cardiologists and in general by primary care and emergency physicians. In the New England Congenital Cardiology Association's prospective evaluation of syncope, this has evolved to be defined as <4 episodes of syncope in the school-age child and adolescent with a clear prodrome, plausible triggers, and generally without injury or incontinence. When seen by a cardiologist, the expectation is that patients have a careful history, an EKG, and cardiac examination. EKGs with clear ventricular hypertrophy, T-wave inversions, QTc >480, Wolff-Parkinson-White (WPW) syndrome, significant AV block, or bundle branch block patterns including Brugada would obviously trigger disease-specific investigations that may appropriately include exercise testing. Similarly those with siblings or parents with genetic heart disease, such as hypertrophic cardiomyopathy (HCM) or long QT syndrome (LQTS), should undergo standard cascade screening.

Exercise-Associated Syncope

Exercise-associated syncope can be subclassified into several different presentations. These are mid-exertional syncope, post-exertional syncope,

M. E. Alexander (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Exercise Physiology, Arrhythmia Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: mark.alexander@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_29

and what may best be classified as exercise-related collapse. The obvious concern here is to identify those with potential causes of subsequent cardiac arrest and to engender appropriate, disease-specific therapy.

Mid-exertional Syncope

Mid-exertional syncope is an accurate description of the most concerning presentation. In this context, the historical concern about identifying cardiac disease is completely supported by experience and data. The presentation is characterized by an abrupt, transient loss of consciousness in the midst of vigorous exercise. Classic and concerning stories are mid-stride collapse during sprint races, or a basketball player collapsing while running down the court. The famous case of Boston Celtics player Reggie Lewis collapsing mid-game is a high-profile adult example. Despite an abnormal tilt test, he subsequently had a fatal cardiac arrest after deferring the implantable cardioverter defibrillator (ICD) recommended by his cardiology team. Miyake [5] and colleagues at Stanford identified 60 children with that presentation. All underwent comprehensive evaluation that always included EKG, echo, and, when no diagnosis was identified, additional testing that generally included exercise testing. They identified 32 with clear cardiac disease (53%). The sequence of testing was typical. Thirteen of the patients were essentially identified with abnormal EKGs: 8 with long QT syndrome (LQTS), 2 with hypertrophic cardiomyopathy (HCM), 2 with Wolff-Parkinson-White (WPW) syndrome, and 1 with catecholaminergic polymorphic ventricular tachycardia (CPVT). Echo confirmed the HCM and identified another with cardiomyopathy. Of the 46 remaining patients, 34 underwent exercise testing. This testing modality identified three additional patients with CPVT. The remaining 15 patients with cardiac rhythm disorders were identified with extended monitoring strategies or EP studies.

A critical aspect of that experience is that nearly half of the cardiac arrhythmia diagnoses required additional testing, beyond EKG and echocardiogram. In addition, 28 (nearly half) of the patients had no disease identified. All had undergone resting EKG and echo. For these patients, the negative exercise test offered substantial reassurance, with highly individualized subsequent evaluation. For the patient with mid-exertional syncope, exercise testing is an effective early diagnostic tool where its ability to identify CPVT (Chap. 32) is particularly useful.

Peri-exertional and Post-exertional Syncope

Dynamic and aerobic exercise such as running results in engagement of the skeletal muscle pump in enhancing systemic venous return. In addition, aerobic exercise is associated with substantial vasodilation. During exercise, those adaptations work together to contribute to overall increase in cardiac output [6]. The effects of the skeletal muscle pump, enhancing venous return and mitigating arterial dilation, combine to help maintain systemic blood pressure. The vasodilation is mediated at multiple levels including the traditional baroreflex mechanisms using the brainstem and substantial local mediation that includes post-exercise hyperemia and post-exercise vasodilation, which in turn are mediated by an apparently central decrease in sympathetic outflow and local histamine release. Analogous to the physiology of typical neurally mediated syncope, some component of hyperventilation and hypocapnea can add cerebral vasoconstriction to the overall physiology. The post-exercise vasodilation can last for up to 20 minutes in controlled settings.

Real-world exercise, of course, also may result in both environmental stresses such as dehydration and heat exhaustion, as well has prolonged exercise past aerobic threshold. Those clinical realities represent additional stresses that can result in non-cardiac, but exercise-related syncope.

With that physiology background, we identify four different patterns of exercise response that

may result in symptoms (Table 29.1). In this context, treadmill testing offers the advantage of providing some orthostatic stress, in addition to the stress of graded exercise. When feasible, expired gas analysis offers multiple additional advantages in evaluating these responses. When exercise stress testing is done specifically to evaluate exertional symptoms, the physiologists may make some alterations to the standard protocol. Early stages may be shortened or skipped, the peak stages may be extended, and following exercise, the patients may be encouraged to remain upright for several minutes prior to sitting down for recovery.

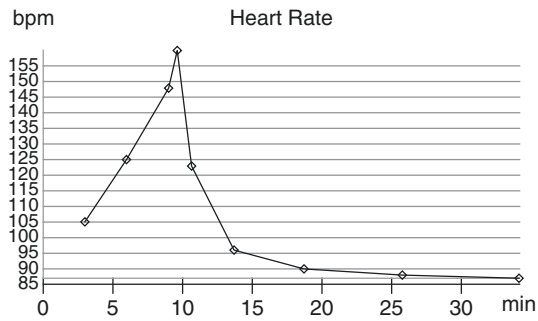
The patterns seen on exercise stress testing are summarized in Table 29.1 and accompanying figures. Exercise-induced hypotension (Fig. 29.1) is a clear decline in blood pressure (10–15 mm Hg) near peak exercise. Blunted blood pressure responses (Fig. 29.2) are defined as a <25 mm Hg rise in systolic BP during a Bruce protocol in adolescents. This is patterned after criteria for hypertrophic cardiomyopathy. (Younger children have lower blood pressure response to exercise and that threshold is therefore inappropriate in the school-age/early adolescent child.) Post-exertional hypotension is a clear (20–30 mm Hg) drop in blood pressure immediately post exercise. Exertional collapse (Fig. 29.3) is defined as partial recreation of symptoms with either respiratory exchange ratio >1.09 (often 1.2 or higher) or a sustained maximal exercise to exhaustion without arrhythmia. The precise cutoffs of these are not well established, and in the pediatric cohort, the range of physical development is sufficient that a fair bit of judgment is required. There are clear overlaps between the patterns. In addition, the physiology can be seen without subjective symptoms. The enhanced afterload and improved venous return that is part of treadmill exercise may partially mitigate the exercise responses that would otherwise promote syncope and pre-syncope. Rarely, post-exercise reflexive syncope can feature the typical hypotension and bradycardia of neurally mediated syncope.

A further advantage of exercise testing in this setting is that the detailed physiologic monitoring may sometimes provide clues for an unusual but reasonable explanation of symptoms. Figure 29.4 represents a cross-country athlete who had repeated episodes of near collapse and confusion, with a pediatric cardiologist evaluating him on the field during these episodes and

Table 29.1 Patterns of exercise-related syncope during exercise testing

	Peak HR	$\dot{V}_{O2}$	RER
Exercise-associated hypotension	NL→ ↑	↓→ NL	↓→ NL
Blunted BP response	NL→ ↑	↓→ NL	↓→ NL
Post-exertional hypotension	NL→ ↑	NL	NL
Exercise-related collapse	NL→ ↑	NL→ ↑	↑

HR heart rate, *BP* blood pressure, *RER* respiratory exchange ratio



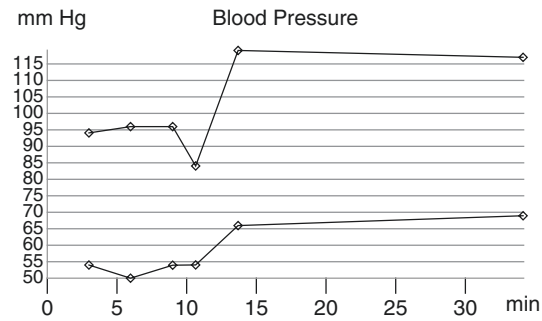


Fig. 29.1 Exercise-induced hypotension. Pattern of exertional hypotension in a 14-year-old female with minimally symptomatic nonobstructive hypertrophic cardiomyopathy. Exercise was limited to a submaximal study by dizziness at just under 10 minutes. Exercise-associated blood pressure failed to augment, and the immediate post-exercise blood pressure was lower before recovering while supine

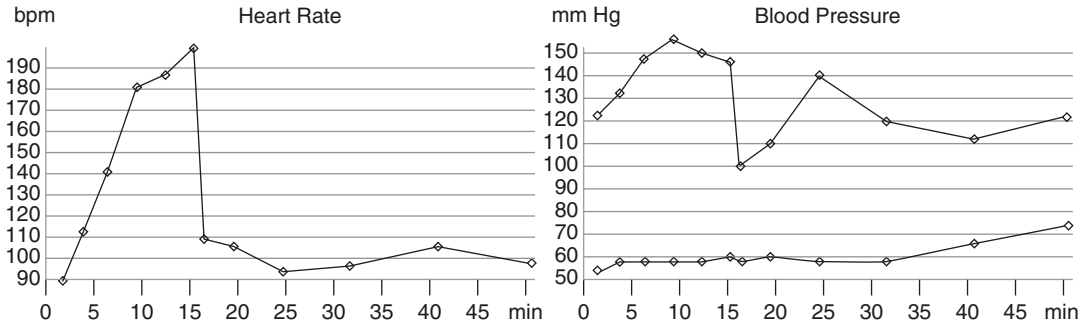


Fig. 29.2 Immediate post-exercise hypotension. A hypermobile adolescent female with multiple exertional symptoms demonstrated substantial immediate post-exercise hypotension, which partially re-created her clinical symptoms. She achieved a 90th percentile performance of 16:25 on a Bruce protocol with a peak blood pressure (BP) of 146/60 followed within a minute by a BP of 100/60 with spontaneous recovery. Symptoms of dizziness and pre-syncopal-like visual changes were reported just prior to termination of active exercise

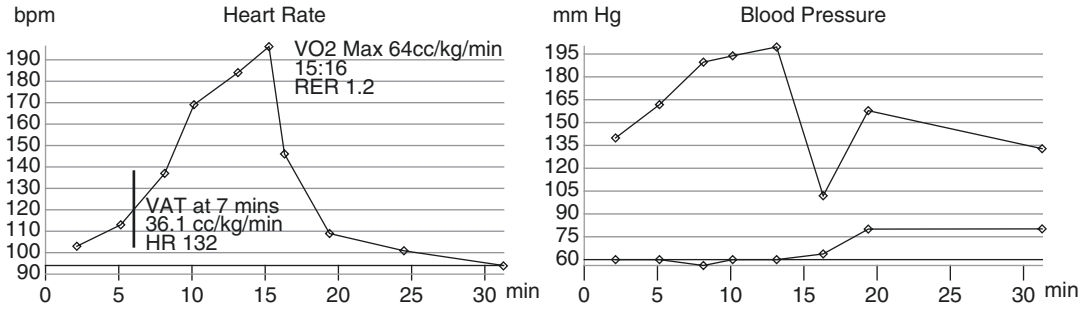


Fig. 29.3 Exertional collapse. Annotated heart rate and blood pressure graphs from a 14-year-old male competitive swimmer with repeated complaints of peak race fatigue. Echo, exam, and lab work were unremarkable. His overall aerobic capacity of 64 ml/kg/min is excellent and consistent with his level of athletic performance. He reaches his aerobic threshold at 7 minutes with a heart rate of 132 (36 cc/kg/min) and continues exercise for another 8 minutes prior to test completion, which had a respiratory exchange ratio (RER) of at least 1.2. During exercise, he was asymptomatic, though he reported dizziness immediately post exercise. He reported that this "wasn't as hard as a race." The post-exertional hypotension here is interpreted as the result of exercising well past his anaerobic capacity rather than an exaggerated tendency toward hypotension seen in the prior examples

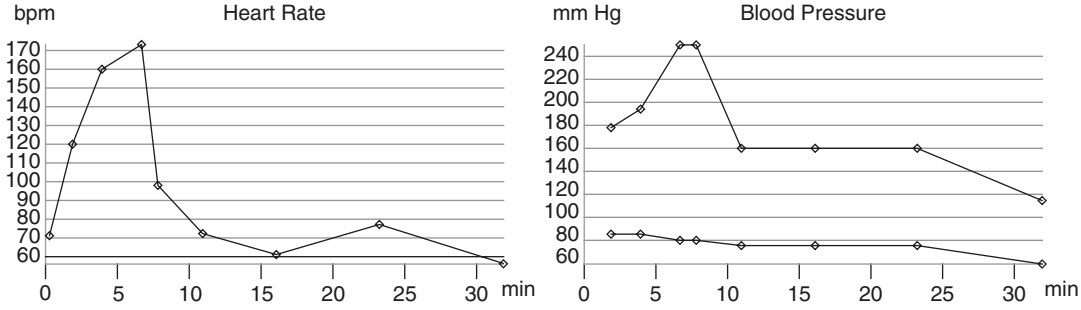


Fig. 29.4 Initial exercise testing on a 16-year-old male cross-country athlete who had recurrent physician-witnessed episodes of stumbling, disorientation, and near-syncope at races. Electrocardiogram (ECG) had demonstrated borderline left ventricular enlargement and there was mild concentric left ventricular (LV) enlargement on echocardiogram (maximum LV wall thickness 1.1 cm/Z = 3.4) and mildly elevated resting blood pressures of 136/53. A Bruce protocol was prematurely terminated for excessive blood pressure (BP) response of 250/80 during stage 4. Subsequent investigations demonstrated essential hypertension, which was effectively treated permitting return to competition. With therapy, he demonstrated a V_{O2} of 66 cc/kg/min and completed Bruce protocols with peak BPs of ~ 200 mm Hg

noting no arrhythmia. With exercise, he demonstrated dramatic exertional hypertension to >250 mm Hg, which triggered effective evaluation and treatment.

Orthostatic Intolerance and Postural Orthostatic Tachycardia

Patients without syncope, but with symptoms suggestive of near syncope, are frequently evaluated in cardiology programs. Like those with syncope, the initial evaluation and management is well established and straightforward. Specific focuses of that evaluation should include evaluation of hypermobility and focused coaching on increased sodium intake, fluid intake, and using isometric maneuvers to augment blood pressure with standing. Some clarity on diagnostic criteria can help in communication with families. For example, both head-up tilt testing and orthostatic vital signs will demonstrate some orthostatic findings in a substantial minority of normal asymptomatic adolescents. In adolescents with low-severity syncope, the 95th percentile for an orthostatic heart rate (HR) change was 35 bpm [1]. This is concordant with heart rate increases during head-up tilt testing, where 42% of asymptomatic normal adolescents have a >30 bpm increase during a 70° head-up tilt test, corresponding to a 95th percentile of a 42 bpm increase. These data, along with multiple other examples, support limiting the diagnosis of postural orthostatic tachycardia syndrome (POTS) to those with repeated HR increases of 40 on 3–5-minute standing tests and classifying those with less substantial changes as orthostatic intolerance.

The pathophysiology of POTS is clearly multifactorial and beyond the scope of this chapter. What is notable is that the physiology of POTS is almost completely mimicked by deconditioning [7] or prolonged space flight [8]. The deconditioning under those circumstances results in decreased blood volume, decreased myocardial dimensions, and other changes in physiology that cause short-term limitations to exercise capacity, potentially amplifying a cycle of disability [9].

For those who are substantially disabled by these symptoms, exercise testing represents a useful adjunct. The goals of exercise testing are both to evaluate $\dot{V}_{O2}$ max and to assess the blood pressure responses to exercise. Our preference is to perform expired gas analysis and a Bruce protocol treadmill, though alternative approaches seem reasonable. Data are somewhat mixed in adults; close to 90% of those with longstanding symptoms will have $\dot{V}_{O2}$ max <90% [10, 11]. Excessive heart rate responses are also frequently found. More convincing is the role that re-training has in improving symptoms. Both organized and self-directed programs using 12–16 weeks of slowly increasing exercise appear to improve symptoms [12]. Re-training may be augmented with supportive medical therapy, with midodrine, fludrocortisone, and beta-blockers being the most popular medications used to support these patients.

Boston Children's Hospital Experience and Context

Syncope is an exceptionally common cardiac complaint, with 7999 distinct patients seen in the Boston Children's Hospital heart center over 12 years. Exercise testing was used in a minority of those patients (4%); the traditional Bruce treadmill protocol was usually employed. An additional 3237 patients were evaluated for dizziness—406 (13%) of those had exercise testing. Exercise-induced hypotension was coded in 391 of those. Similar numbers had some exertional arrhythmia, often trivial.

Management was quite variable, and was based primarily on symptom severity and level of concern about potentially more serious conditions. Management included traditional recommendations for syncope/pre-syncope (hydration, sodium loading, and environmental precautions), drugs such as midodrine to augment vascular tone, and recommendations to focus on effective exercise management. Implantable loop recorders were particularly useful for repeated episodes of poorly explained syncope, resulting in positive or negative diagnoses in more than half.

Conclusion

- Patients with life-threatening conditions that present with syncope can be recognized promptly and appropriately with history, physical EKG, and echocardiography.
  - Once diseases are recognized, exercise testing may be part of disease characterization and management.
- Exercise testing has a critical role in patients with high-risk histories of syncope, to evaluate for CPVT and other unusual arrhythmia syndromes.
- Most patients with low-severity, typical syncope will not benefit from exercise testing (or any substantial testing).
- For patients with more problematic symptoms, exercise testing represents a relatively low barrier test that can identify multiple contributors to symptoms. This includes
  - Deconditioning
  - Abnormal or potentially abnormal blood pressure responses
  - Incidental or potentially important arrhythmias
- The differences between normal and abnormal exercise responses in those with potential orthostatic syndrome overlap with normal physiology. Testing always needs to be interpreted in context.

References

1. Paris Y, Toro-Salazar OH, Gauthier NS, Rotondo KM, Arnold L, Hamershock R, et al. Regional implementation of a pediatric cardiology syncope algorithm using standardized clinical assessment and management plans (scamps) methodology. J Am Heart Assoc. 2016;5(2):2016.
2. Johnson ER, Etheridge SP, Minich LL, Bardsley T, Heywood M, Menon SC. Practice variation and resource use in the evaluation of pediatric vasovagal syncope: are pediatric cardiologists over-testing? Pediatr Cardiol. 2014;35(5):753–8.
3. Batra AS, Balaji S. Usefulness of tilt testing in children with syncope: a survey of pediatric electrophysiologists. Indian Pacing Electrophysiol J. 2008;8(4):242–6.
4. Lewis DA, Zlotocha J, Henke L, Dhala A. Specificity of head-up tilt testing in adolescents: effect of various degrees of tilt challenge in normal control subjects. J Am Coll Cardiol. 1997;30(4):1057–60.
5. Miyake CY, Motonaga KS, Fischer-Colbrie ME, Chen L, Hanisch DG, Balise RR, et al. Risk of cardiac disease and observations on lack of potential predictors by clinical history among children presenting for cardiac evaluation of mid-exertional syncope. Cardiol Young. 2015;17:1–7.
6. Halliwill JR, Buck TM, Lacewell AN, Romero SA. Postexercise hypotension and sustained postexercise vasodilatation: what happens after we exercise? Exp Physiol. 2013;98(1):7–18.
7. George SA, Bivens TB, Howden EJ, Saleem Y, Galbreath MM, Hendrickson D, et al. The international pots registry: evaluating the efficacy of an exercise training intervention in a community setting. Heart Rhythm. 2016;13(4):943–50.
8. Wieling W, Halliwill JR, Karemaker JM, Wieling W, Halliwill JR, Karemaker JM. Orthostatic intolerance after space flight. [comment]. J Physiol. 2002;538 (Pt 1):1.
9. Fu Q, Levine BD. Exercise and the autonomic nervous system. Handb Clin Neurol. 2013;117:147–60.
10. Parsaik A, Allison TG, Singer W, Sletten DM, Joyner MJ, Benarroch EE, et al. Deconditioning in patients with orthostatic intolerance. Neurology. 2012;79(14):1435–9.
11. Burkhardt BEU, Fischer PR, Brands CK, Porter C, Weaver AL, Yim PJ, et al. Exercise performance in adolescents with autonomic dysfunction. J Pediatr. 2011;158(1):15–9.
12. Fu Q, Levine BD. Exercise in the postural orthostatic tachycardia syndrome. Auton Neurosci Basic Clin. 2015;188:86–9.

30

Exercise Stress Testing: Diagnostic Utility in the Evaluation of Long QT Syndrome

Stephanie F. Chandler, Robyn J. Hylind, and Dominic J. Abrams

Introduction

Congenital long QT syndrome (LQTS), an inherited disorder of ventricular repolarization, is characterized by a prolonged QT interval and T-wave morphological changes on the surface electrocardiogram with associated symptoms of syncope, seizures, cardiac arrest, and sudden death [1, 2]. With an estimated prevalence of 1:2000, it is an important cause of sudden death in the young population [3, 4]. Symptoms relate to a characteristic life-threatening ventricular arrhythmia, torsades de pointes (TdP), initially termed due to an apparent pattern of rotating QRS complexes around an imaginary baseline [5]. Symptoms may occur at any age from fetal life onward. Although a significant proportion of individuals genetically predisposed to LQTS may never experience any clinical manifestations, symptomatic presentation in childhood typically identifies those at higher risk for further cardiac events [2, 6, 7]. The clinical diagnosis is based on multiple electrocardiographic parameters, as well as personal and family history [8]. However, due to the low penetrance of the disorder, exercise testing has been increasingly recognized as part of the diagnostic algorithm to unmask cases of latent LQTS.

S. F. Chandler (✉)
Department of Cardiology, Ann and Robert H. Lurie Children's Hospital, Chicago, IL, USA

Department of Pediatrics, Northwestern Feinberg School of Medicine, Chicago, IL, USA

R. J. Hylind
Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

D. J. Abrams
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Inherited Cardiac Arrhythmia Program, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: dominic.abrams@cardio.chboston.org

Genetics

The biological underpinning of LQTS is genetically encoded abnormalities in cardiac ion channels or associated cellular proteins. To date, sequence variants in 17 genes encoding varying cardiomyocyte proteins have been identified in patients with LQTS, designated LQT1 through LQT17 [9]. LQTS type 1 (LQT1), LQTS type 2 (LQT2), and LQTS type 3 (LQT3) associated with genes encoding potassium (*KCNQ1* – KvLQT1; *KCNH2* – hERG) and sodium (*SCN5A* – NaV1.5) cellular channels, respectively, account for 90% of patients with an identifiable genetic etiology [10].

Exercise Testing and Long QT Syndrome

The diagnostic workup for LQTS includes a comprehensive personal and family history, including the nature and triggers of any symptoms in the

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_30

patient or family members. The resting 12-lead electrocardiogram (EKG) is used to determine the QT interval, which defines cardiac repolarization, and the T-wave morphology [8]. The QT interval should be measured in lead II or V5, from the onset of the Q wave to the intersection of the steepest downslope of the T-wave with the isoelectric baseline, and corrected for heart rate using Bazet's formula (QTc). Although there is no clear relationship between QT interval duration and genotype, ST segment and T-wave morphological abnormalities have been associated with particular genotypes [11]. An analysis of 248 genetically sequenced LQT patients highlighted some typical electrocardiographic patterns: LQT1 carriers demonstrated normal or broad-based T-wave pattern consistent with the homogenous action potential prolongation caused by affecting I_{ks} cells. LQT2 carriers demonstrated a bifid T-wave pattern secondary to increased transmural dispersion due to greater increase in action potential duration in the M cells of the myocardium. Finally, LQT3 patients had a late peaked T-wave thought to be due to delay in opening of the sodium channels and hence prolongation of depolarization [12].

In patients with overt QT prolongation and classical symptoms, the diagnosis is evident [13, 14]. Similarly, in patients with a normal EKG and no family history of LQTS or sudden death, there may be little reason to consider the diagnosis. However, given the recognized low penetrance of these mutations, further diagnostic investigations are frequently necessary if the initial testing is ambiguous. Electrocardiographically, there is significant overlap in QT duration between those with concealed LQTS and unaffected individuals. Several studies of families affected by LQTS using genetic analysis have shown that as many as 75% of individuals with the familial variant have QT intervals within the normal range, likely related to a combination of variable penetrance, the effect of modifying genes, and individual variability in QT duration [15–20]. Exercise stress testing (EST) therefore has become an important diagnostic tool [2, 21, 22]; and in those old enough to cooperate, EST should be part of the diagnostic work-up, looking specifically for a maladaptive QT response during the recovery phase from exercise. EST—be it on a treadmill or bicycle—has been demonstrated to be useful in both pediatric and adult patients. Genotype-specific repolarization responses to EST in patients with LQT1 and LQT2 have emerged [22–29].

Prior to EST, brisk standing may also demonstrate limited QT accommodation in patients with LQTS. Studies in adult patients have demonstrated significant QT prolongation and T-wave morphological changes when compared to controls. However, in children, there may be significant QT prolongation, even in normal subjects, to a level that may lead to an inappropriate diagnosis of LQTS [8, 17, 30–35]. This QTc prolongation in unaffected children may be substantial and arises primarily from a posture-related increase in heart rate; the absolute QT does not change significantly (Fig. 30.1).

Several investigators have systematically examined the response of normal subjects to exercise. In one of the largest studies, Berger et al. evaluated 94 healthy volunteers aged 8–17 years with resting EKG and exercise testing to assess normal ranges for QT and corrected QT interval in recovery phase. These authors reported a nearly linear inverse relationship between heart rate and QT interval in recovery with a mean increase of 15 ms in the QT interval per 19 beat decrease in heart rate, with the 98th percentile for corrected QT intervals during 4–6 minutes of recovery ranging from 482 to 491 ms. [36] These findings supported other earlier observations with albeit smaller patient numbers [25, 37]. In the normal heart, the QT interval shortens in response to adrenergic stimulation. This shortening is determined by the depolarizing effects of voltage-gated (L-type) calcium channel stimulation, opposed by cyclic-AMP-induced phosphorylation of Iks that enhances K+ efflux and repolarization. In LQT1 where KvLQT1 function is impaired, the offsetting of L-type Ca++ depolarization is reduced, leading to pathologic QT prolongation [35]. Experimental data in canine wedge preparations found that drug-induced I_{ks} blockade alone (as would be expected in LQT1 patients) did not induce transmural dispersion of

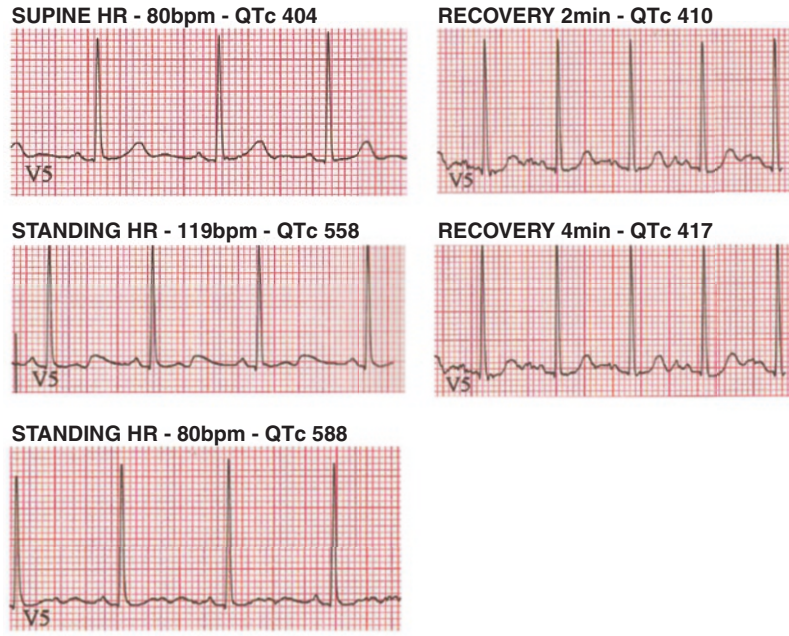


Fig. 30.1 Abnormal QT response to standing. Electrocardiographic images (lead V5) from a 13-year-old male were investigated following the sudden death of his mother, who had no prior symptoms or diagnosis and a negative autopsy. On standing, there was marked QT prolongation of the QT interval with morphological changes, although at baseline and in recovery from exercise, his corrected QT intervals were normal. This was not felt to represent long QT syndrome

repolarization (TDR) between cell types. Addition of catecholaminergic stress with isoproterenol, however, induced action potential duration (APD) shortening in epicardial and endocardial but not M cells, leading to significant transmural dispersion of repolarization and torsades des pointes (TdP). This cellular electrophysiology could be successfully blocked by propranolol. These data would appear to explain the adrenergic basis of arrhythmia in LQT1 and the successful effect of beta-blockers [30]. However, in comparison to animal modeling, human subjects with LQTS may demonstrate a variety of maladaptive responses to exercise: The QT interval may fail to shorten, may lengthen with exertion and at increased heart rates, and may be prolonged during the recovery phase after exercise.

In 1995, as the genetic basis for LQTS was discovered, several studies reported an association of certain T-wave morphological patterns with the 3 LQTS types [32, 38]. In addition, studies in both adult and pediatric patients have demonstrated genotype-specific repolarization responses with EST [2, 21, 22, 28]. For instance, in a study of 82 patients genetically predisposed to LQTS, Takenaka et al. [27] demonstrated that a modified Bruce protocol used in combination with qualitative assessment of T-wave morphology was useful in identifying patients with LQT1, who experienced marked QTc prolongation during exercise. The structural or functional anomalies of KvLQT1, the potassium channel protein associated with LQT1, resulted in decreased potassium conductance (Ik_s), which, during sympathetic activation, led to attenuated shortening of the QT interval [24], in addition to decreased chronotropic response during exercise, followed by augmented lengthening of the QT interval as the heart rate declined during early and late (1 and 4 minutes) recovery after exercise (Figure 30.2a, b) [27, 29]. In adult patients with LQT1, there is decreased accommodation of the QT interval during exercise compared to LQT2 patients, with marked QTc prolongation by virtue of higher heart rates. In comparison, only a modest change in the QTc interval was observed in LQT2 and LQT patients with no identified genotype [22]. Horner et al. found that paradoxical QTc prolongation during the recovery phase (QTc $\geq$ 460 ms) distinguishes LQT1 patients from controls even when the resting QTc is within normal limits with a

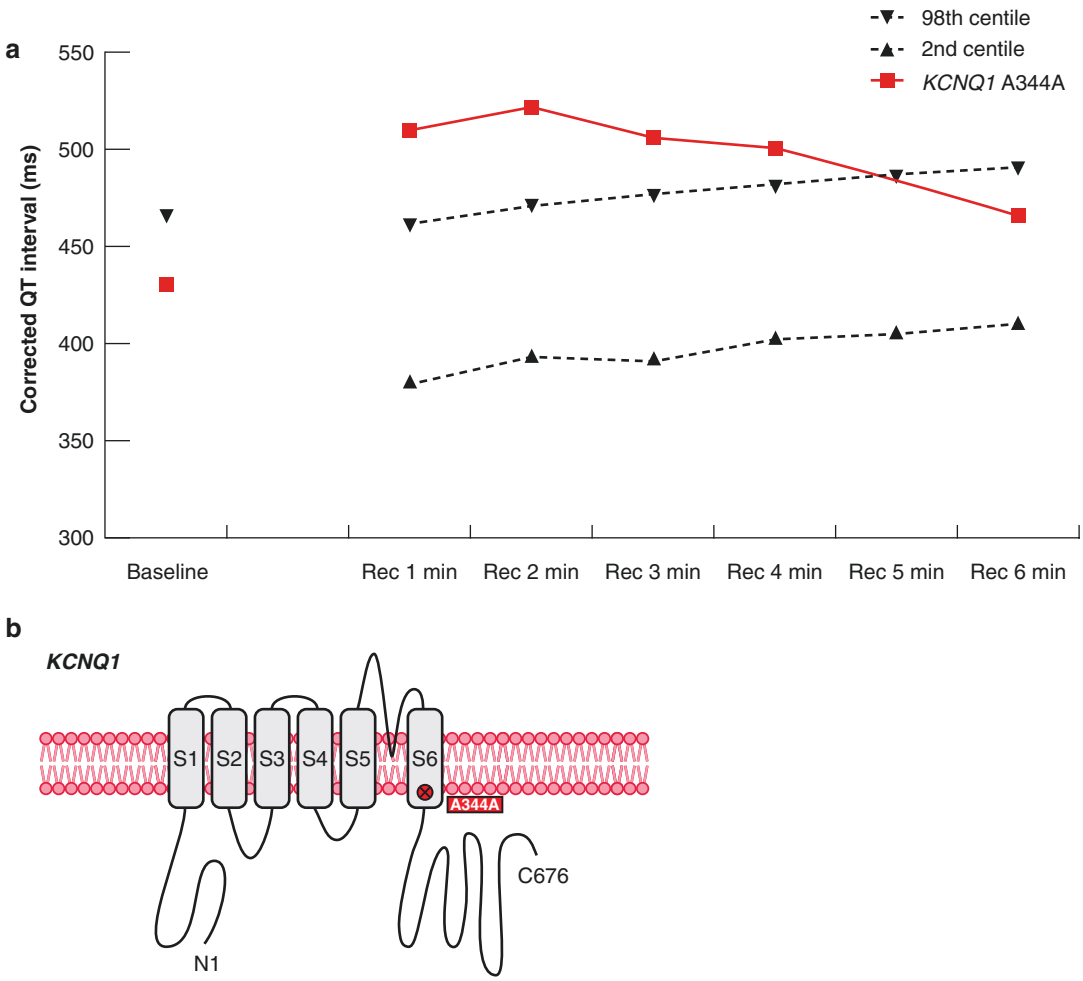


Fig. 30.2 The QT response in recovery from exercise in a patient with long QT syndrome type 1. The corrected QT interval at baseline and in recovery from exercise is shown for a 14-year-old investigated for a family history of long QT syndrome, with a variant KCNQ1 A344A segregating in the family. A344A is a synonymous mutation, with a nucleotide substitution at the last position in exon within the canonical splice region, which results in exon-skipping and likely haploinsufficiency by nonsense-mediated mRNA decay of the mutant transcript. (**a**) The patient's values are shown (red line) together with the 2nd and 98th percentiles for controls (black dashed line) derived from Berger et al. [35]. At baseline, his QTc is normal (427 ms), but in early recovery, there is significant prolongation with a gradual return to the normal range over 6 minutes, consistent with *KCNQ1*-mediated long QT 1 syndrome. (**b**) The topology of *KCNQ1* is depicted together with the position of A344A in S6 transmembrane domain

sensitivity of 90%, specificity of 92%, positive predictive valve of 74%, and negative predictive value of 97% [21]. Additionally, a Δ(Delta) QTc ≥ 30 ms defined as QTc 3 minute recovery – QTc baseline supine reveals LQTS1 with a sensitivity of 83%, specificity of 93%, positive predictive valve of 76%, and negative predictive value of 95% [21]. In children, late recovery phase at 7 minutes has been suggested to better predict the LQTS and a recovery Δ(Delta)QTc (7 minutes – 1 minute) >30 ms differentiated LQT2 versus LQT1 [2].

Patients with LQT2 can have notable QT interval shortening and a normal chronotropic response during exercise [28, 39]. However, they typically display an exaggerated QT hys-

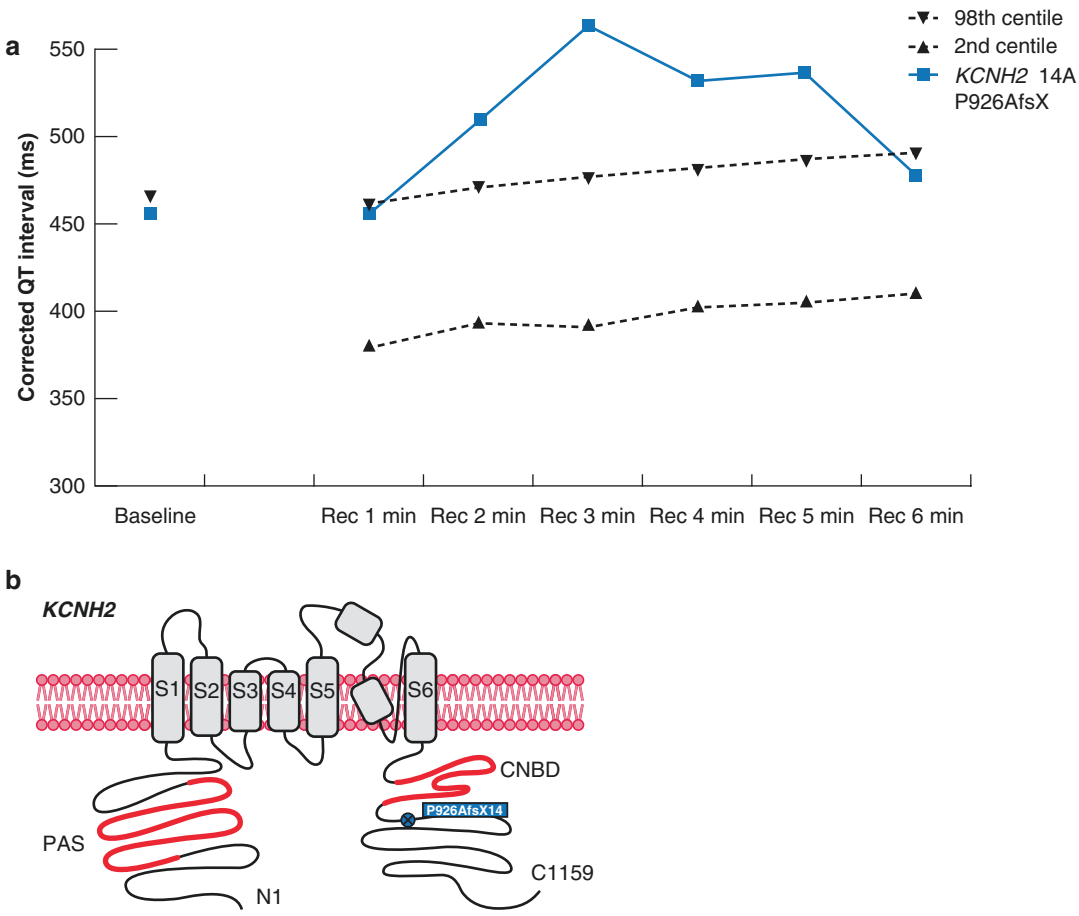


Fig. 30.3 The QT response in recovery from exercise in a patient with long QT syndrome type 2. The corrected QT interval at baseline and in recovery from exercise is shown for a 25-year-old investigated for a recent history of syncope and seizures. (**a**) The patient's values are shown (blue line) together with the 2nd and 98th percentiles for controls (black dashed line) derived from Berger et al. [35]. At baseline, his QTc is normal (457 ms) and remains within normal limits at 1 minute in recovery but shows marked prolongation in later recovery, consistent with *KCNH2*-mediated long QT 2 syndrome. Genetic testing identified a frameshift variant in KCNH2, c.2775dupG; p.Pro926AlafsX14, a single-nucleotide duplication leading to a change in the reading frame and premature stop codon. KCNH2 shows considerable constraint and intolerance to loss of function. This variant has been reported in multiple families with long QT syndrome with significant segregation. Functional studies have shown a reduction of hERG current in channels with this mutation, related to haploinsufficiency secondary to nonsense-mediated decay of the mutant transcript. This variant is absent from control populations in the gnomAD database. (**b**) The topology of *KCNH2* is depicted together with the position of A344A in S6 transmembrane domain

teresis, defined as the QT interval difference between exercise and 2 minutes into recovery at similar heart rates (within 10 bpm) (Figure 30.3a, b) [22, 33]. In LQT2 and LQT3, both QTc and Δ(Delta)QTc may decrease during exercise [21]. In younger patients, although the QTc intervals shortened with exercise and in early recovery, in patients with LQT2, the QTc prolongs in later recovery (defined as 7 and 9 minutes) and values converge with those of patients with LQT1 [2].

These, largely concordant observations in LQT1 and LQT2, are distinct from LQT3. Persistent sodium conductance secondary to SCN5A sequence variants underlie LQT3, which account for approximately 10% of LQTS [40]. Clinically, events in patients with LQT3 are more frequent with sleep and rest, as opposed to

emotion/startle and exercise with LQT1 and LQT2 [41]. Studies with LQT3 are smaller, but consistently demonstrate both more QTc shortening with exercise and less QTc prolongation with recovery. In addition, although at baseline corrected QT measurements had similar average values between the three subtypes (LQT1, LQT2, LQT3) as demonstrated by Schwartz et al. in a series of 517 patients, [41] in a small series of 16 genotyped LQTS patients compared to 21 unrelated healthy subjects, the QTc at 4 minutes in recovery in patients with LQT3 were not significantly higher than in age-matched controls (Figure 30.2a, b).

Questions regarding the effects of beta-blockade on QTc during exercise testing are often raised. Multiple studies have found that the patterns of QT interval response during exercise and recovery are not significantly altered by treatment with beta-blockers [2, 21, 28, 42]. However, EST is routinely employed in patients with established LQTS to assess the heart rate response to exercise and objectively evaluate the adequacy of beta-blocker therapy.

In summary, multiple studies in adults and a few in pediatric patients have demonstrated the value of performing EST as a diagnostic tool in the evaluation of patients with suspected LQTS. As LQTS demonstrates reduced penetrance and many patients are asymptomatic, affected individuals with LQTS can be erroneously considered unaffected if only clinical features and resting EKG are utilized for diagnostic purposes. EST and—specifically—QTc interval prolongation during recovery after EST has been demonstrated to be a sensitive screening test for LQTS [43]. Genotype-specific responses to EST have been demonstrated; prior work has shown that there exists a paradoxical increase in corrected QT interval during the recovery phase of treadmill stress testing that can distinguish LQTS—particularly those patients with LQT1—from others including controls [2, 21, 22]. Patients with LQT1 often display a longer QT interval at maximum heart rate when compared to LQT2 patients, while LQT3 patients appear to shorten their corrected QT intervals at maximum heart rates and are at higher risk at longer cycle lengths [41]. Even with a nondiagnostic QTc at rest, prolongation of the QTc in recovery from exercise, in addition to a Δ(Delta) QTc ≥ 30 ms during recovery periods may help distinguish LQT1 from others [2, 21]. In children, late recovery phase at 7 minutes—as children often have a more gradual deceleration in their heart rates during the recovery phase of EST—has been suggested to better predict the LQTS, and a recovery Δ(Delta) QTc (7 minutes – 1 minute) >30 ms differentiated LQT2 from LQT1 [2]. Finally, while EST protocols for the evaluation of LQTS in adult cohorts are often limited to the first 5 minutes of recovery, as previously stated, children often have a more gradual heart rate deceleration during the recovery phase of the EST. An extended recovery phase may therefore be preferable to assess the repolarization response after exercise in children [2].

Conclusion

Take-Home Points

1. Our approach to evaluating the patient with suspected congenital LQTS involves multiple steps including clinical and family history, resting EKG for evaluation of corrected QT intervals in addition to T-wave morphology and exercise stress testing. For those patients with combinations of markedly prolonged QTc at rest and family history of LQTS, exercise testing may offer further phenotypic characterization, but is not part of confirming the diagnosis.
2. For those patients in whom the diagnosis is in question, EST is a helpful adjunct to better define the phenotype and help differentiate between LQT1 and LQT2.
3. While QT intervals can increase with brisk standing in adult patients with LQTS, in pediatric patients, the QT interval increases with standing in healthy unaffected children, limiting the utility of this test in distinguishing between affected and unaffected pediatric patients.
4. Although the QT interval response during exercise and recovery has not been found to be significantly altered by beta-blocker treatment, peak exercise heart rate is evaluated

routinely in patients with established LQTS to help assess adequacy of beta-blocker.
5. Both treadmill and cycle exercise are reasonable approaches to EST in potential LQTS.
6. Final conclusions regarding a diagnosis of LQTS will always require a combination of resting EKG, personal and family history, genetic testing (when applicable), and EST results.

References

1. Ackerman MJ, Clapham DE. Ion channels–basic science and clinical disease. N Engl J Med. 1997;336:1575–86.
2. Aziz PF, Wieand TS, Ganley J, Henderson J, Patel AR, Iyer VR, et al. Genotype- and mutation site-specific QT adaptation during exercise, recovery, and postural changes in children with long-QT syndrome. Circ Arrhythm Electrophysiol. 2011;4:867–73.
3. Tester DJ, Ackerman MJ. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. J Am Coll Cardiol. 2007;49:240–6.
4. Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, et al. Prevalence of the congenital long-QT syndrome. Circulation. 2009;120:1761–7.
5. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004;350:1013–22.
6. Liu JF, Jons C, Moss AJ, McNitt S, Peterson DR, Qi M, et al. Risk factors for recurrent syncope and subsequent fatal or near-fatal events in children and adolescents with long QT syndrome. J Am Coll Cardiol. 2011;57:941–50.
7. Zareba W, Moss AJ, Locati EH, Lehmann MH, Peterson DR, Hall WJ, et al. Modulating effects of age and gender on the clinical course of long QT syndrome by genotype. J Am Coll Cardiol. 2003;42:103–9.
8. Schwartz PJ, Ackerman MJ. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. Eur Heart J. 2013;34:3109–16.
9. Schwartz PJ, Ackerman MJ, George AL, Wilde AAM. Impact of genetics on the clinical management of channelopathies. J Am Coll Cardiol. 2013;62:169–80.
10. Ruan Y, Liu N, Napolitano C, Priori SG. Therapeutic strategies for long-QT syndrome: does the molecular substrate matter? Circ Arrhythm Electrophysiol. 2008;1:290–7.
11. Zareba W. Genotype-specific EKG patterns in long QT syndrome. J Electrocardiol. 2006;39:S101–6.
12. Zhang L, Timothy KW, Vincent GM, Lehmann MH, Fox J, Giuli LC, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. Circulation. 2000;102:2849–55.
13. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. Circulation. 1993;88(2):782–4.
14. Hofman N, Wilde AAM, Tan HL. Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: do we need a scoring system? Eur Heart J. 2007;28:1399–9.
15. Zareba W. Challenges of diagnosing long QT syndrome in patients with nondiagnostic resting QTc. J Am Coll Cardiol. 2010;55:1962–4.
16. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. Circulation. 1999;99:529–33.
17. Goldenberg I, Mathew J, Moss AJ, McNitt S, Peterson DR, Zareba W, et al. Corrected QT variability in serial electrocardiograms in long QT syndrome: the importance of the maximum corrected QT for risk stratification. J Am Coll Cardiol. 2006;48:1047–52.
18. Malik M, Färbom P, Batchvarov V, Hnatkova K, Camm AJ. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart. 2002;87:220–8.
19. Vincent GM, Schwartz PJ, Denjoy I, Swan H, Bithell C, Spazzolini C, et al. High efficacy of beta-blockers in long-QT syndrome type 1: contribution of noncompliance and QT-prolonging drugs to the occurrence of beta-blocker treatment "failures". Circulation. 2009;119(2):215–21.
20. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. N Engl J Med. 1992;327:846–52.
21. Horner JM, Horner MM, Ackerman MJ. The diagnostic utility of recovery phase QTc during treadmill exercise stress testing in the evaluation of long QT syndrome. Heart Rhythm. 2011;8:1698–704.
22. Wong JA, Gula LJ, Klein GJ, Yee R, Skanes AC, Krahn AD. Utility of treadmill testing in identification and genotype prediction in long-QT syndrome. Circ Arrhythm Electrophysiol. 2010;3(2):120–5.
23. Katagiri-Kawade M, Ohe T, Arakaki Y, Kurita T, Shimizu W, Kamiya T, Orii T. Abnormal response to exercise, face immersion, and isoproterenol in children with the long QT syndrome. Pacing Clin Electrophysiol. 1995;18(12 Pt 1):2128–34.
24. Swan H, Viitasalo M, Piippo K, Laitinen P, Kontula K, Toivonen L. Sinus node function and ventricular repolarization during exercise stress test in long QT syndrome patients with KvLQT1 and HERG potassium channel defects. J Am Coll Cardiol. 1999;34(3):823–9.
25. Swan H, Toivonen L, Viitasalo M. Rate adaptation of QT intervals during and after exercise in children with congenital long QT syndrome. Eur Heart J. 1998;19:508–13.
26. Paavonen KJ, Swan H, Piippo K, Hokkanen L, Laitinen P, Viitasalo M, et al. Response of the QT interval to mental and physical stress in types LQT1 and LQT2 of the long QT syndrome. Heart. 2001;86(1):39–44.

27. Takenaka K, Ai T, Shimizu W, Kobori A, Ninomiya T, Otani H, et al. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long-QT syndrome. Circulation. 2003;107(6):838–44.
28. Chattha IS, Sy RW, Yee R, Gula LJ, Skanes AC, Klein GJ, et al. Utility of the recovery electrocardiogram after exercise: a novel indicator for the diagnosis and genotyping of long QT syndrome? Heart Rhythm. 2010;7(7):906–11.
29. Sy RW, van der Werf C, Chattha IS, Chockalingam P, Adler A, Healey JS, et al. Derivation and validation of a simple exercise-based algorithm for prediction of genetic testing in relatives of LQTS probands. Circulation. 2011;124(20):2187–94.
30. Shimizu W, Antzelevitch C. Cellular basis for the EKG features of the LQT1 form of the long-QT syndrome: effects of beta-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. Circulation. 1998;98:2314–22.
31. Moss AJ, Long QT. Syndrome. JAMA. 2003;289:2041–4.
32. Dausse E, Berthet M, Denjoy I, André-Fouet X, Cruaud C, Bennaceur M, et al. A mutation in HERG associated with notched T waves in long QT syndrome. J Mol Cell Cardiol. 1996;28(8): 1609–15.
33. Krahn AD, Klein GJ, Yee R. Hysteresis of the RT interval with exercise: a new marker for the long-QT syndrome? Circulation. 1997;96:1551–6.
34. Dionne A, Fournier A, Dahdah N, Abrams D, Khairy P, Abadir S. Dynamic QT interval changes from supine to standing in healthy children. Can J Cardiol. 2018;34(1):66–72.
35. Vyas H, Hejlik J, Ackerman MJ. Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. Circulation. 2006;113:1385–92.
36. Berger WR, Gow RM, Kamberi S, Cheung M, Smith KR, Davis AM. The QT and corrected QT interval in recovery after exercise in children. Circ Circ Arrhythm Electrophysiol. 2011;4(4):448–55.
37. Benatar A, Decraene T. Comparison of formulae for heart rate correction of QT interval in exercise EKGs from healthy children. Heart. 2001;86:199–202.
38. Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, et al. EKG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation. 1995;92(10):2929–34.
39. Schwartz PJ, Priori SG, Locati EH, Napolitano C, Cantù F, Towbin JA, et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na+ channel blockade and to increases in heart rate. Implications for gene-specific therapy. Circulation. 1995;92(12):3381–6.
40. Tester DJ, Ackerman MJ. Genetics of long QT syndrome. Methodist Debakey Cardiovasc J. 2014;10:29–33.
41. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. 2001;103(1):89–95.
42. Kaltman JR, Ro PS, Stephens P, McBride MG, Cohen MI, Tanel RE, et al. Effects of beta-adrenergic antagonists on the QT measurements from exercise stress tests in pediatric patients with long QT syndrome. Pediatr Cardiol. 2003;24(6):553–8.
43. Sy RW, van der Werf C, Chattha IS, Chockalingam P, Adler A, Healey JS, et al. Derivation and validation of a simple exercise-based algorithm for prediction of genetic testing in relatives of LQTS probands. Circulation. 2011;124(20):2187–94.

Wolff-Parkinson-White Syndrome

31

Tam Dan N. Pham and Mark E. Alexander

Introduction

Wolff-Parkinson-White (WPW) syndrome is a ventricular pre-excitation syndrome affecting approximately 1–3 in 1000 individuals and carries a low, but clinically important, risk of sudden cardiac death. The clinical presentation can vary from asymptomatic WPW to cardiac arrest as the sentinel event. As more electrocardiograms (EKGs) are obtained as part of stimulation medication clearance and screening for sports, the incidental finding of isolated ventricular pre-excitation, or WPW pattern, increasingly leads to referral of patients for evaluation of WPW. In response, practice guidelines have been developed for the management of patients with asymptomatic WPW. These guidelines include noninvasive and invasive testing and have ascribed an important role to exercise testing [1–3].

T. D. N. Pham
Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

M. E. Alexander (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Exercise Physiology, Arrhythmia Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: mark.alexander@cardio.chboston.org

Electrocardiogram Findings in Wolff-Parkinson-White

The core physiology of WPW is an accessory pathway that permits atrioventricular (AV) conduction independent of the AV node. WPW syndrome is characterized by atrioventricular reciprocating tachycardia with a sinus EKG pattern of bundle branch block (BBB) and a short PR interval. Some cardiologists make the distinction between a WPW pattern on EKG and WPW syndrome with the WPW pattern used to describe the EKG findings without clinical manifestations. The term "pre-excitation" is defined by early ventricular activation occurring ahead of normal AV nodal conduction. As the atrial depolarization wavefront approaches the ventricles, it may advance over the accessory pathway, normal AV node, or both. Conduction over the accessory pathway is rapid and pre-excites a focal ventricular segment. This region of early activation generates activated ventricular myocardium without the typical delays associated with His-Purkinje conduction. This creates the short PR interval and characteristic delta wave seen on EKGs. For most patients, some portion of ventricular activation will still occur over the normal AV nodal-His pathway with the resting EKG manifesting a fusion between pre-excitation and normal depolarization sequence [4, 5].

Depending on the location of the accessory pathway along the tricuspid or mitral valve annulus, EKG patterns in WPW syndrome can be variable.

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_31

Several algorithms have been developed to provide more exact estimates of accessory pathway location based on delta wave polarity or QRS shape, such as the Arruda et al. algorithm [6]. At the most simplistic level, the activation vector in left-sided APs travels away from the left and toward the right, resulting in negative delta waves in left-sided EKG leads (I, aVL, V5-V6) and positive delta waves in right-sided leads (aVR, V4R-V1). The right ventricle is still activated over the normal AV node, but only after the usual nodal time delay; thus, the QRS morphology is reminiscent of right BBB, though it is often remarkably normal. The opposite is true for right-sided APs, which can mimic a left bundle branch pattern [4, 6].

Fasciculoventricular pathways (FVPs) are defined as an atypical accessory connection between the His bundle and the upper ventricular septum, and can cause subtle pre-excitation on EKG. FVPs exhibit antegrade-only conduction with a fixed short HV interval, and do not have the ability to support a reciprocating tachycardia or rapid conduction of atrial fibrillation. These pathways are benign and, according to Josephson, can be considered as merely an electrocardiographic curiosity [7, 8]. They are antegrade-only connections that are completely dependent upon effective AV node conduction. Hence, they neither can support AV reciprocating tachycardia, nor can they permit rapidly conducting pre-excited atrial fibrillation. Further, their anatomic linkage to the AV node makes ablation of them unwise. They are important largely because confident recognition of an FVP may permit clinicians to forego further diagnostic testing.

Atrioventricular pathways, previously called Mahaim pathways, are slowly conducting, antegrade-only, pre-excitation syndromes that are typically associated with normal PR intervals. While they are important to recognize, they are not typically confused with the more common WPW patterns.

Accessory Pathway Characteristics and Clinical Manifestation

Accessory pathways are thought to be embryological remnants resulting from failure of resorption of the myocardial syncytium at the annulus fibrosis of the AV valves during fetal development. They are located along the AV groove and typically conduct electrical impulses more rapidly than the AV node, leading to the characteristic EKG findings in WPW. Accessory pathways that have retrograde conduction properties can support supraventricular tachycardia (SVT) by providing a reentrant circuit involving both the AV node-His axis and the accessory pathway. SVT can be orthodromic (narrow, or "usual complex") or, less commonly, antidromic (wide complex). Orthodromic SVT results from normal antegrade conduction over the AV node-His axis and retrograde conduction over the accessory pathway. Alternatively, antidromic SVT results from antegrade conduction over the accessory pathway and retrograde conduction over the AV node [4].

Clinical Presentation

Although many patients seek therapy for symptoms of supraventricular tachycardia (SVT) related to WPW, an estimated 50% of pediatric WPW patients are asymptomatic when identified. Presenting symptoms, when present, include palpitations, chest pain, dizziness, or presyncope. The most worrisome presentation is syncope or aborted sudden cardiac death (SCD) as the first manifestation of WPW syndrome. The risk of SCD, including resuscitated sudden death, is estimated to be between 0.05% and 0.5% per year. The mechanism of SCD is thought to be rapid antegrade accessory pathway conduction of atrial fibrillation (AF) (Fig. 31.1), provoking ventricular fibrillation (VF) [1, 2].

Risk Stratification

Ideally, the management of school-age children, adolescents, and young adults with WPW should be guided by risk stratification [2, 3, 5]. For those with documented SVT and pre-excitation, risk stratification usually occurs as part of an invasive electrophysiology (EP) study where the goal is effective elimination of the pathway. There are alternative approaches to those without symptoms.

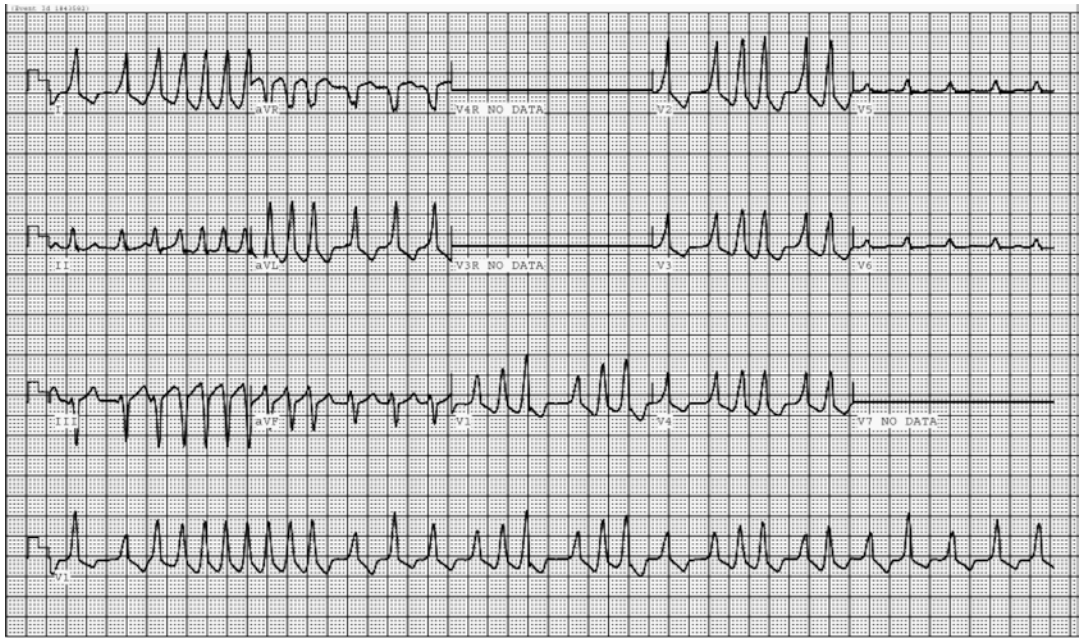


Fig. 31.1 12-lead EKG at ½ and ¼ standard of rapid pre-excited atrial fibrillation in a 14-year-old with previously asymptomatic WPW. The shortest pre-excited RR interval is 211 msec. Exercise testing showed persistent pre-excitation to a maximal heart rate of 184. At subsequent EP study, his accessory pathway effective refractory period was 800/390 with a shortest pre-excited RR interval in pacing of 290 msec

Any comprehensive evaluation of the "risk" of WPW needs to take into account symptoms, the ability to have SVT, antegrade risk characteristics (within the limitations of confidence that modern analysis has demonstrated), and the risk of therapy. A history of documented SVT, plausible symptoms of palpitations, and potential cardiac syncope are all critical parts of the symptomatic risk profile.

Anatomic Risk

Anatomic risk relates to the risks that are accrued during ablation. This can be broadly divided into the low-risk right posterior to right anterior-lateral tricuspid annulus where there is virtually no risk of injury to the AV node, no risk of stroke, and no significant risk of coronary injury. Common left lateral locations involve ablation within the systemic circulation and the need for transeptal puncture or retrograde approaches. These procedures carry a small but clear risk of cerebral vascular events and anatomic injury; these anatomic risks can be categorized as mildly increased. Septal pathway ablations have variable risks of injury to the AV node, coronary sinus, and coronary arteries. While the risks are low, septal pathways represent higher-risk ablation targets. Exercise testing does not inform those risks. Algorithms, such as Arruda's [6], may provide some noninvasive information regarding anatomic risk, but are reliable in younger children with more rapid AV nodal conduction.

Electrophysiologic Risk

Exercise testing can help inform the assessment of electrophysiologic antegrade risk characteristics. The intent of risk stratification in patients with asymptomatic WPW is to identify which individuals are at risk for a lethal cardiac arrhythmia by assessing the antegrade conduction properties of the accessory pathway. The critical and obligate condition for VF is the presence of a short antegrade accessory pathway effective refractory period (APERP), which would allow

for rapid conduction of AF. The EKG measuring the shortest pre-excited R-R interval during clinical AF is a "true" assessment of the anterograde characteristics of the accessory pathway, though the measurement of the Shortest Pre-Excited R-R Interval (SPERRI or SPRRI) has long been used as an operational proxy for that clinical finding. An SPERRI of 220–250 msec has been more commonly seen in patients who have experienced cardiac arrest [2]. We have generally classified electrophysiological antegrade risk as high or low based on a SPERRI of ≤250 msec, and >350 msec, respectively, with those in between considered intermediate. Because clinical cardiac arrest and clinical pre-excited atrial fibrillation are uncommon, most of the literature has been based on invasive testing. Thus, the primary goal of noninvasive testing is to determine which asymptomatic patients will need to have an invasive EP study.

Exercise Testing

The simplest form of risk stratification utilizes noninvasive testing with a Holter monitor (for younger patients), or exercise testing to observe for loss of pre-excitation. Loss of pre-excitation during exercise has been proposed as a surrogate method of assessing the antegrade APERP. This is a relatively rare phenomenon, occurring in only ~15% of patients with WPW who undergo exercise testing. Patients who demonstrate abrupt loss of pre-excitation during exercise may be classified as "low risk," and potentially avoid the need for invasive testing. The notion is that an abrupt loss at a heart rate of 150 correlates with an SPRRI of 400 msec and an abrupt loss at even 180 bpm would be an SPRRI of 320 msec. However, several limitations exist with exercise testing alone.

Systematic reviews correlating EP studies with exercise testing have shown that the clinical implications of an abrupt loss of the delta wave are not straightforward. A prospective study conducted by Gaita et al. studied exercise and pharmacologic testing as methods to identify patients with WPW syndrome who otherwise met criteria for electrophysiological high-risk accessory pathway by invasive testing (SPERRI during AF ≤250 or APERP ≤250). Persistence of pre-excitation on exercise test showed a sensitivity of 96%, but specificity of only 17% in identifying high-risk patients. The positive predictive value was 40%, and the negative predictive value was 88%. Interestingly, the patient who had the shortest SPERRI in this series (180 msec) was the only "high-risk" patient to demonstrate loss of pre-excitation on exercise testing [9]. In 90 consecutive patients who underwent both exercise testing and invasive EP studies at Boston Children's Hospital, abrupt disappearance of pre-excitation during exercise testing occurred in only about 15% of patients (Fig. 31.2). These individuals had a statistically longer APERP (348 msec ±47 msec range 260–420 msec) compared to those with persistent pre-excitation (322 ± 56, range 200–540). Hence, abrupt loss of pre-excitation was noted in children whose APERP was noted to be as short as 260 msec [10]. Moreover, a blinded review in 57 patients in the ETT-EPS group found an 86–91% interobserver agreement between the pairs of blinded and clinical reviews ($p < 0.001$ for all paired comparisons). Despite this high agreement, the independent reviewers either disagreed or classified the results as uncertain in 9 (16%) of these studies. Of the tests that were discordant or

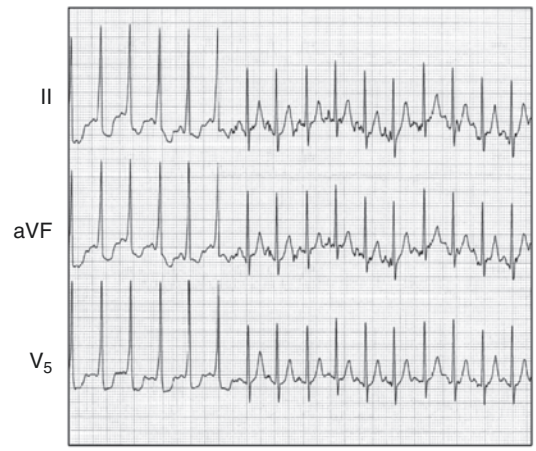


Fig. 31.2 Obvious and abrupt loss of pre-excitation at an HR of 180

uncertain to at least one reader, 8 (89%; $p = 0.001$) were left sided (Fig. 31.3). Taken together, these data support using clear unambiguous loss of pre-excitation, such as intermittent pre-excitation at rest, as a statistical marker of lower risk, but not an absolute marker (Table 31.1). Sharing the uncertainty can permit families who have a child with WPW to make informed decisions about the risk/benefits of invasive EP study and ablation and the risk/benefits of observation. It must also be noted that, although loss of pre-excitation may have implications regarding the risk for SCD, it does not imply that a patient is not at risk for SVT.

These limitations are very similar to those that are encountered with every measure of antegrade risk assessment. Intermittent pre-excitation on Holter monitoring is seen in ~13% of patients with WPW. While those patients had longer mean refractory periods (340 msec) compared to those with persistent pre-excitation at rest (310 msec), in both groups, approximately 10–12% of patients had short refractory periods, defined as ≤250 msec [11]. Even invasive EP studies, the "gold standard," have substantial limitations. In a case-control study of 96 patients with life-threatening events, 22 of 60 who underwent effective assessment prior to ablation (37%) did not meet the accepted criteria of rapid conduction <250 msec [12].

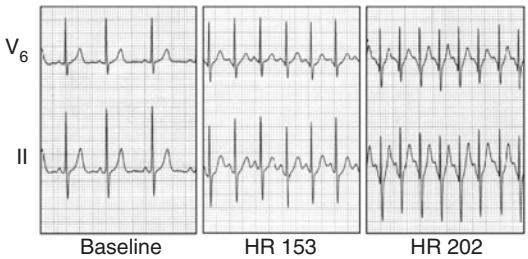


Fig. 31.3 More subtle pre-excitation in a 12-year-old with SVT who was judged to have loss of pre-excitation by an HR of 150 by 2 examiners and uncertain by 1 examiner. At EPS, a single left-sided accessory pathway with an APERP of 500/260 was identified

The reality is that loss of pre-excitation with exercise testing, intermittent pre-excitation, and EP study-based refractory periods each predict a group with longer refractory periods. At the same time, these tests are incomplete at assessing the "at-risk" physiology, and a substantial minority (10–12% for exercise testing) will have potentially dangerous pathways, despite reassuring testing.

Fasiculoventricular pathways are increasingly recognized during EP study and represent an innocent physiology that carries no risk of either SVT or cardiac arrest. The delta wave is generally subtle (Fig. 31.4). There is no anticipated change during exercise testing (though that can be a challenging conclusion in some patients given the narrow QRS). Consultation with an

Table 31.1 Test characteristics of exercise findings in predicting antegrade accessory pathway effective refractory period (APERP); 90 patients with graded exercise testing and intracardiac electrophysiological (EP) studies. APERP measured at baseline conduction. Persistent pre-excitation has a 100% sensitivity in identifying APERP ≤250 msec, 11% of those children with persistent pre-excitation will have APERP ≤250 msec. Abrupt loss of pre-excitation was reassuring with a positive predictive value of 100% to identify those with refractory periods ≥250 msec. Using a more stringent definition of low antegrade risk, abrupt loss of pre-excitation had a 67% positive predictive value for effective refractory periods

Utility of persistent pre-excitation								
APERP	N	Persistent	Loss	Sensitivity	Specificity	PPV	NPV	LR+
≤320	45	41	4	91%	18%	53%	67%	1.1
≤250	8	8	0	100%	15%	10%	100%	1.2
≤220	4	4	0	100%	5%	14%	100%	1.0
Utility of loss of pre-excitation								
APERP	N	Persistent	Loss	Sensitivity	Specificity	PPV	NPV	LR+
>320	45	37	8	18%	91%	67%	53%	2.0
≥250	82	70	12	15%	100%	100%	10%	∞
>220	86	79	12	14%	100%	100%	5%	∞

PPV positive predictive value; *NPV* negative predictive value; *LR+* likelihood ratio positive

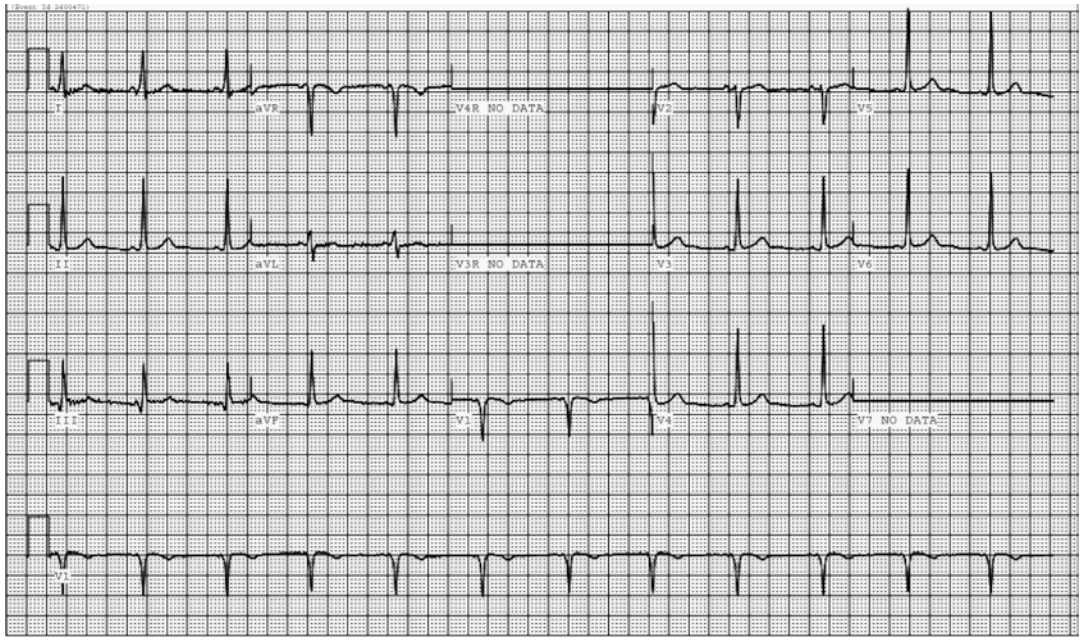


Fig. 31.4 Subtle pre-excitation associated with a documented fasciculoventricular pathway with obligate AV node conduction

electrophysiologist can help develop strategies for confirming that diagnosis [13].

Symptomatic Patients and Exercise Testing

The current recommendations are that symptomatic patients with WPW undergo catheter ablation if they have life-threatening symptoms, or if these symptoms are refractory to age-appropriate medical management [2]. Additionally, as ablation confers a high success rate with relatively low risk, older symptomatic patients should be considered for an ablation soon after diagnosis. For these symptomatic patients, exercise testing offers little advantage as it does not provide additional diagnostic data. For symptomatic patients without low-risk characteristics on exercise testing, medical management is unattractive, even if effective in controlling SVT symptoms. Further, data do not support medical management, particularly with beta-blockers, limiting the risk of pre-excited atrial fibrillation or cardiac arrest.

Conclusion

The clinical presentation of WPW syndrome varies from asymptomatic WPW to sudden cardiac death. Practice guidelines have been developed for WPW syndrome, primarily for the management of asymptomatic WPW. These guidelines focus on sequential risk stratification and aim to assess antegrade conduction properties of the accessory pathway, with the goal of identifying those who may be at risk for sudden death. Abrupt loss of pre-excitation at physiologic heart rates or intermittent pre-excitation at those same rates identifies a group of patients more likely to be at lower risk of rapidly conducting pre-excited atrial fibrillation. However, limitations related to the physiology of this disorder, interobserver reliability, and the inability of exercise testing to provide information on retrograde pathway conduction all lead to only a minority (10–20%) of patients having invasive EP studies deferred on the basis of exercise data, patient history, and clinician and patient choice.

Conclusions Include

1. Older symptomatic patients should undergo invasive EP study and consideration of ablation. Exercise testing for symptomatic patients offers little additional information.
   (a) Deferring procedures is appropriate in infants and younger children.
   (b) Those with life-threatening symptoms should be referred for EP consultation at any age.
2. Abrupt loss of pre-excitation during exercise is a relatively rare phenomenon. Although it implies a lower-risk cohort in some of these patients, SPERRI may be as low as ~260 msec, at/near the margin of high risk. While the classification of patients as low risk is imperfect, this finding can contribute to deferring more formal EP study and ablation.
3. There are significant limitations of exercise testing, which include:
   (a) Variability on what heart rates can be reliably viewed as "low risk."
   (b) Interobserver variability and difficulty in interpreting "loss of pre-excitation" at higher heart rates. This is particularly true of left-sided accessory pathways.
   (c) Response to exercise testing does not give data to predict the likelihood of developing SVT.
   (d) Patients with fasciculoventricular pathways (FVPs) will persist with subtle pre-excitation throughout the study. Exercise testing offers no useful information with this physiology.
   (e) Though exercise testing may allow some patients to be identified as "low risk," low positive predictive value renders exercise testing a poor way of assessing for "high-risk" pathways.

Patients who cannot be clearly classified as "low risk" on exercise testing should consider a more formal EP study, which is often combined with an attempt at catheter ablation.

References

1. Munger TM, Packer DL, Hammill SC, Feldman BJ, Bailey KR, Ballard DJ, et al. A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted County, Minnesota, 1953–1989. Circulation. 1993;87(3):866–73.
2. Pediatric, Congenital Electrophysiology S, Heart Rhythm S, American College of Cardiology F, American Heart A, American Academy of P, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS). Heart Rhythm. 2012;9(6):1006–24.
3. Cohen M, Triedman J. Guidelines for management of asymptomatic ventricular pre-excitation: brave new world or Pandora's box? Circ Arrhythm Electrophysiol. 2014;7(2):187–9.
4. Walsh EP, Triedman JK, Berul CI. Cardiac arrhythmias. In: John Keane DF, Lock J, editors. Nadas' pediatric cardiology. 2nd ed. Philadelphia: Elsevier; 2006. p. 162–8.
5. Triedman J, Perry J, Van Hare G. Risk stratification for prophylactic ablation in asymptomatic Wolff-Parkinson-White syndrome. [comment]. N Engl J Med. 2005;352(1):92–3.
6. Arruda MS, McClelland JH, Wang X, Beckman KJ, Widman LE, Gonzalez MD, et al. Development and validation of an ECG algorithm for identifying accessory pathway ablation site in Wolff-Parkinson-White syndrome. J Cardiovasc Electrophysiol. 1998;9(1):2–12.
7. Kottkamp H, Hindricks G, Shenasa H, Chen X, Wichter T, Borggrefe M, et al. Variants of pre-excitation--specialized atriofascicular pathways, nodofascicular pathways, and fasciculoventricular pathways: electrophysiologic findings and target sites for radiofrequency catheter ablation. J Cardiovasc Electrophysiol. 1996;7(10):916–30.
8. Josephson ME. Clinical cardiac Electrophysiology. Techniques and interpretation. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 419–21.
9. Gaita F, Giustetto C, Riccardi R, Mangiardi L, Brusca A. Stress and pharmacologic tests as methods to identify patients with Wolff-Parkinson-White syndrome at risk of sudden death. Am J Cardiol. 1989;64(8):487–90.

10. Bershader RS, et al. Exercise testing for risk assessment in pediatric Wolff-Parkinson-White syndrome. Heart Rhythm. 2007;4:138–9.
11. Mah DY, Sherwin ED, Alexander ME, Cecchin F, Abrams DJ, Walsh EP, et al. The electrophysiological characteristics of accessory pathways in pediatric patients with intermittent preexcitation. Pacing Clin Electrophysiol. 2013;36(9):1117–22.
12. Etheridge SP, Escudero CA, Blaufox AD, Law IH, Dechert-Crooks BE, Stephenson EA, et al. Life-threatening event risk in children with Wolff-Parkinson-White syndrome: a Multicenter International Study. JACC Clin Electrophysiol. 2018;4(4):433–44.
13. O'Leary ET, Dewitt ES, Mah DY, Gauvreau K, Walsh EP, Bezzerides VJ. Differentiation of fasciculoventricular fibers from anteroseptal accessory pathways using the surface electrocardiogram. Heart Rhythm. 2019. pii: S1547-5271(19)30119-5. https://doi.org/10.1016/j.hrthm.2019.02.011.

32 Exercise Testing in the Management of Arrhythmias

Audrey Dionne, Edward T. O'Leary, Shankar Baskar, Vassilios J. Bezzerides, and Mark E. Alexander

Overview

Exercise stress testing (EST) is an attractive tool in the ongoing management of patients either with suspicion or established diagnosis of arrhythmias, cardiomyopathies, and genetic diseases with specific arrhythmia risks. Rapid access to 12-lead electrocardiogram (EKG), the ability to correlate rhythm, and, for many patients, the ability to encourage exercise beyond their usual activities are substantial advantages. Those advantages are tempered by generally marginal test characteristics, which, as always, are informed by the remainder of the clinical scenario. At the clearest end of the spectrum, for patients with supraventricular tachycardia (SVT), exercise testing has low sensitivity, low specificity, and rarely offers useful information. The other end is patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) for whom exercise testing is a controlled way to confirm the clinical phenotype and assess therapy. While suspected based on history and normal EKG and echocardiogram, the diagnosis is confirmed by exercise testing. For virtually every other question, EST is part of characterizing a patient's physiology.

There are relatively clear trade-offs in technical choices with EST. Bicycle ergometry will reliably produce EKG tracings with less artifact; however, peak heart rate (HR) and peak blood pressure (BP) are lower. At Boston Children's Hospital, when the primary indication is evaluation of arrhythmia, standard Bruce protocols are used in the overwhelming majority of cases. Local equipment and practice may vary, with no compelling data to argue against practice variation.

A. Dionne · E. T. O'Leary · S. Baskar
Arrhythmia Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: Audrey.dionne@cardio.chboston.org; Edward.oleary@cardio.chboston.org; Shankar.baskar@cardio.chboston.org

V. J. Bezzerides · M. E. Alexander (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Arrhythmia Service, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: vassilios.bezzerides@cardio.chboston.org; mark.alexander@cardio.chboston.org

Evaluation of Bradycardia

Sinus Node Dysfunction

Sinus node dysfunction (SND) refers to abnormal impulse generation and/or conduction out of the sinoatrial node manifested on the surface EKG as sinus bradycardia, sinus pauses, sinus

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_32

arrest, sinus node exit block, or inadequate escape rhythms. When SND is accompanied by clinical symptoms such as fatigue, lightheadedness, dyspnea on exertion, and/or syncope, it is referred to as sick sinus syndrome. In addition to a comprehensive history, physical examination, and ambulatory heart rate monitoring, exercise testing can assist in identifying SND, particularly chronotropic incompetence, in patients without symptoms at rest.

In children and adolescents, congenital heart disease (CHD) is a major cause of SND, which can present primarily as an anatomic anomaly or more commonly postoperative sequelae. D-looped transposition of the great arteries (D-TGA) repaired via the Mustard or Senning atrial switch procedure is the archetypal lesion associated with SND, with more than half of the patients affected and 13% of patients requiring a permanent pacemaker by the tenth postoperative year [1, 2]. Patients with D-TGA who have undergone atrial switch procedures have reduced exercise capacity, primarily driven by chronotropic incompetence, when compared not only to healthy controls but also to contemporary cohorts who had an arterial switch procedure [3, 4]. While atrial switch procedures have since largely been abandoned for the treatment of D-TGA, it is still used in the treatment of other CHDs and there are numerous adults with that surgical anatomy. SND affects at least 9% of patients with single ventricle heart disease and Fontan palliation. Permanent pacemaker implantation is the most common cardiac procedure in this population of patients [5, 6]. Superior sinus venosus defects are also commonly associated with postoperative SND, with 5% of patients requiring a permanent pacemaker following repair [7]. Serial exercise testing can provide objective evidence of SND and thus should be considered in the long-term follow-up of these patients. Exercise testing should primarily focus on the peak HR response, and can inform sources of exercise limitation when combined with expired gas analysis. Exercise testing should be combined with other monitoring strategies, such as Holter, to evaluate for long pauses and low resting heart rates. Either physiology can produce symptoms and be an indication for pacing. In the absence of symptoms, limited exercise heart rate responses are not an indication for pacing [8].

Patients with symptomatic SND can be managed with atrial or dual-chamber pacing depending on the primary electrophysiologic manifestation of their sinus node disease and the status of their intrinsic atrioventricular (AV) conduction. In the setting of normal AV conduction, a single-chamber atrial demand pacing system (AAI) is an appropriate choice with the addition of rate responsiveness (AAIR) if chronotropic incompetence is also present. Rate responsiveness (also termed rate adaptation or rate modulation) provides physiologic chronotropy, leading to augmented cardiac output during periods of increased physical activity. Standardized exercise testing protocols are used for optimization of rate-responsive pacing, capable of delineating appropriate chronotropic responses at the onset of exercise, during moderate exertion, at peak exertion, and during recovery. Rate-responsive systems utilize artificial sensors that modulate the pulse generator pacing rate by measuring various surrogate parameters for metabolic demand. Activity sensors comprised of piezoelectric crystals or accelerometers respond rapidly to movement and thus are effectively programmed during exercise testing. They are limited, however, by both their inability to sense the oxygen debt accrued during sustained aerobic exercise and by oversensing movements that should not warrant increased cardiac output, such as laughing and coughing. These limitations would result in either inappropriately slow or fast chronotropic responses, respectively. Similarly piezoelectric sensors will underestimate activity during indoor cycling or other activities with no movement where the pacemaker is located (abdomen/upper chest). Metabolic sensors that sense minute ventilation, central venous temperature, venous pH, or QT interval are available and can help avoid abrupt decreases in paced heart rates following cessation of exercise. However, how important these distinctions are in clinical practice is unclear. Virtually, all pacemakers and standard defibrillators have some rate-response features built in. The clinical data to support these somewhat proprietary choices for rate response are, not surprisingly, limited.

Programming rate-responsive therapy in patients with SND following an atrial switch procedure for D-TGA can present unique challenges due to their anatomic and electrophysiologic abnormalities. Transitioning to an accelerated junctional rhythm during exercise can be detrimental due to the loss of AV synchrony. Accelerated junctional rhythm may be associated with atrial undersensing, resulting in apparently random atrial output that is seen during EST. Moreover, the transvenous pacing site is the morphologic left atrium, which in combination with extensive atrial scarring often causes substantial intra-atrial conduction delay. This frequently results in intra-atrial block and a pseudo-Wenckebach effect at elevated heart rates, effectively producing symptoms consistent with pacemaker syndrome, and thereby obviating the benefit of AAIR programming with high upper rates [9]. *Pacemaker syndrome* refers to signs and symptoms caused by inadequate timing of atrial and ventricular contractions in pacemaker patients and is discussed in further detail below. Programming a high activity threshold and rapid rate responsiveness, with the aid of formal exercise testing, can often overcome this problem and result in maintaining a paced rhythm at maximal exercise.

Clinical decision-making to place a pacemaker for bradycardia focuses first and foremost on symptoms, followed by the presence of bradycardia-facilitated tachycardia. The newest guidelines emphasize that there is no lower rate or pause duration that is an absolute indication for pacing [10]. Ambulatory monitoring is typically the first line of surveillance, but exercise testing can be particularly useful in evaluating complaints of exercise intolerance in at-risk patients, and in evaluating the programming choices in response to symptoms.

Atrioventricular Block

Atrioventricular block (AVB) is defined as abnormally prolonged or interrupted transmission of an atrial impulse to the ventricles secondary to functional or anatomic disease within the conduction system. It is further categorized by whether all (first-degree AVB), some (second-degree AVB), or no (third-degree AVB) atrial impulses conduct to the ventricles. First-degree AVB and second-degree Mobitz 1 AVB are typically localized to the AV node and can frequently be seen in healthy children and adolescents, particularly in highly conditioned athletes with increased vagal tone. Pathologic causes of higher-grade AVB include Lyme carditis, cardiomyopathy, certain types of muscular dystrophy, ischemia, myocarditis, endocarditis, and surgical trauma following repair of congenital heart disease. The role of exercise testing in the evaluation of the various degrees of AVB is discussed below.

In first-degree AVB, there is delayed but not interrupted conduction between the atria and ventricles. Some atrial impulses are not conducted to the ventricles in second-degree AVB, which is further classified as Mobitz 1 (Wenckebach) and Mobitz 2. Mobitz 1 AVB consists of progressive PR interval prolongation with an eventual nonconducted P wave, followed by resumption of sinus rhythm with the first PR interval being shorter than the previously conducted P wave prior to block. Both first-degree AVB and Mobitz 1 AVB are most often caused by vagally mediated functional conduction delay or block at the level of the AV node. Exercise testing can assist in the differentiation between benign first-degree AVB or Mobitz 1 AVB due to increased vagal tone, from that caused by true injury to the AV node. In the case of first-degree AVB or Mobitz 1 AVB, there is normalization of AV conduction with PR interval shortening, while in AV nodal injury, there is progression to higher-degree AVB at increasing sinus rates. Rarely, marked AV nodal delay with PR intervals exceeding 300 milliseconds can produce a pseudopacemaker syndrome that shares the similar pathophysiology to that seen with VVI pacing and retrograde VA conduction. Exercise testing can be used to demonstrate symptoms consistent with pacemaker syndrome in the setting of severely prolonged PR intervals, which is a class II indication for permanent pacemaker implantation [8]. Patients with Mobitz 1 AVB that normalizes during exercise are rarely symptomatic and thus do not require permanent pacing. EST in those patients is an effective and reassuring tool to evaluate the physiology.

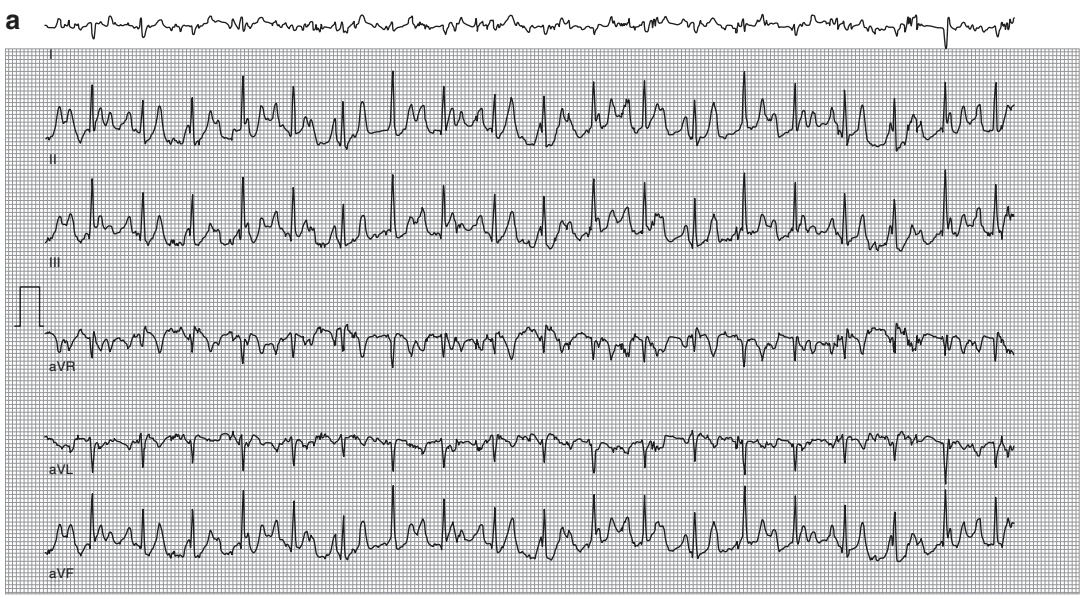
Unlike first-degree AVB and Mobitz 1 AVB, Mobitz 2 AVB is rarely present in patients without underlying cardiac disease and is almost always secondary to conduction system injury within the His-Purkinje system. This manifests as a nonconducted P wave preceded by stable PR intervals, with high-grade AVB defined as two or more consecutive nonconducted P waves. Often, there is concomitant bundle branch block. Third-degree AVB is defined by AV dissociation where no atrial impulses are transmitted to the ventricles. Decisions surrounding permanent pacemaker implantation in second-degree (both Mobitz 1 and 2), high-grade AVB, and third-degree AVB are made in accordance with published societal guidelines and rarely require exercise testing as part of their diagnostic workup [8]. A notable exception will be the asymptomatic patient with well-established congenital 2nd or 3rd degree block. For those patients, a reasonable exercise response, combined with minimal dilation and normal valve and ventricular function on echocardiogram, can permit deferring permanent pacemaker implant (Fig. 32.1a, b).

Pacing options in patients with significant AV node disease include ventricular demand (VVI) and dual-chamber (DDD) devices, with or without the addition of rate responsiveness if chronotropic incompetence is also present. While VVI systems require only a single lead and provide emergency backup pacing from intermittent severe bradycardia, they do not maintain AV synchrony and thus risk the development of pacemaker syndrome. *Pacemaker syndrome* occurs due to inappropriate timing of atrial and ventricular contractions and may manifest as dizziness, neck pulsations, palpitations, syncope, and congestive heart failure. Lack of AV synchrony results in reduction of cardiac output by as much as 20% due to the loss of contribution from atrial systole. Cannon A waves result from atrial contraction against closed AV valves with subsequent abrupt increases in central venous pressure, blunting the usual baroreceptor-mediated vasopressor response and producing systemic hypotension. Continuous EKG monitoring with simultaneous blood pressure measurements during exercise testing can capture these abrupt decreases in systemic blood pressure associated with the onset of AV asynchrony. Pacemaker syndrome in the setting of VVI pacing can occur due to either complete AV dissociation with random AV asynchronous events, or more commonly 1:1 retrograde ventriculoatrial (VA) conduction with fixed AV asynchrony [11]. Given the risk of pacemaker syndrome in patients with VVI pacing and 1:1 VA conduction, dual-chamber pacing modes are often preferable in the absence of chronic atrial tachycardias.

DDD pacing systems carry their own risk of programming complications. Sudden 2:1 AVB with an abrupt decrease in the ventricular rate can occur during peak exercise if the programmed upper rate interval (URI or URL- upper rate limit) equals the total atrial refractory period (TARP). A Wenckebach upper rate response can prevent this issue but requires the URI to be programmed longer than the TARP. This can be accomplished by decreasing the sensed AV delay or postventricular atrial refractory period (PVARP), either at rest or adaptively with increasing atrial rates. Ideally, these issues are considered prior to exercise testing, but practically, many are uncovered by testing.

Both DDD and VVIR pacing modes improve hemodynamics and exercise capacity compared to VVI pacing alone. VVIR systems are simpler to insert, require less intensive follow-up, and are less expensive than their DDD counterparts, though they carry the physiologic cost of losing AV synchrony and a higher risk of developing pacemaker syndrome. The maintenance of AV synchrony with DDD pacing has not been demonstrated to improve survival in adults with high-degree AVB without preexisting congestive heart failure [12]. Exercise capacity and quality-of-life metrics are reduced in adults paced VVIR compared to those paced DDD, likely due to the development of pacemaker syndrome; exercise performance and symptoms are no different between these 2 pacing modes when complete AV and VA blocks are present [13–15]. In patients with otherwise favorable physiology, VVIR pacing can permit outstanding exercise capacity and simplify care (Fig. 32.2).

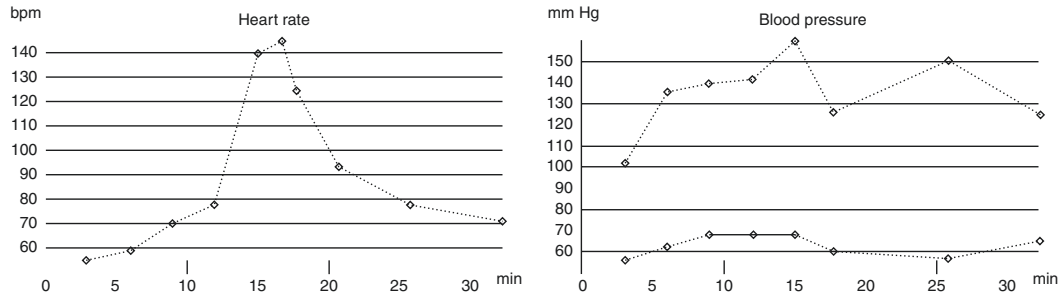
Congenital complete heart block (CCHB) in a structurally normal heart is a rare condition



Metabolic Cart

Peak work rate		**Peak VE**	82.8 L/min
% Predicted work rate	(nl > 85)	**Breathing reserve**	42% (nl 25–45)
Peak relative VO2	39.6 ml/kg/min	**VE/VCO2 slope***	28 (nl < 29)
% Predicted peak VO2	91% (nl > 85)	**Relative VO2 at VAT**	21.3 ml/kg/min
Peak PER*	1.13	**VAT/predicted peak VO2**	49% (nl 40–70)
Peak O2 pulse*	19.1 ml/beat	**Heart rate at VAT**	84 bpm
% Predicted peak O2P	153% (nl > 85)	**HR at VAT/predicted peak**	43%
Peak heart rate	116 bpm	**PETO2 at VAT**	107 mm Hg (nl 95–110)
% Predicted peak HR	59% (nl > 85)	**PETCO2 at VAT**	37 mm Hg (nl 37–43)
Heart rate increase	Depressed	**PETCO2 during exercise**	Normal
Peak RR	47 breaths/min	**O2 pulse at VAT/Pred**	113%
Peak VT	1.75 L	**Anaerobic threshold time**	04:53 min
% Baseline FVC	46% (nl 45-55)		

Fig. 32.1 Exercise testing in heart block without permanent pacing. (**a**) Peak heart rate EKG of a patient with long-standing idiopathic AVB who has a brisk resting junctional escape, runs 5Ks without difficulty, and demonstrates normal left ventricular echocardiogram parameters. She demonstrates a junctional escape mechanism with scattered ventricular premature beats. (**b**) Accompanying heart rate trends and expired gas analysis of the same patient demonstrating compensatory increases in O2 pulse and effective $\dot{V}_{O2}$ max



Metabolic cart			
Peak work rate		**Peak VE**	126 L/min
% Predicted work rate	(nl > 85)	**Breathing reserve**	24% (n 25–45)
Peak relative VO2	55.7 ml/kg/min	**VE/VCO2 slope***	29 (nl < 29)
% Predicted peak VO2	112% (nl > 85)	**Relative VO2 at VAT**	28.8 ml/kg/min
Peak PER*	1.14	**VAT/Predicted peak VO2**	58% (nl 40–70)
Peak O2 Pulse*	24.4 ml/beat	**Heart rate at VAT**	58 bpm
% Predicted peak O2P	152% (nl > 85)	**HR at VAT/predicted peak**	34%
Peak heart rate	150 bpm	**PETO2 at VAT**	106 mm Hg (nl 95–110)
% Predicted peak HR	74% (nl > 85)	**PETCO2 at VAT**	39 mm Hg (nl 37–43)
Heart rate increase	Depressed	**PETCO2 during exercise**	Normal
Peak RR	51 breaths/min	**O2 pulse at VAT/Pred**	173%
Peak VT	2.45L	**Anaerobic threshold time**	05:44 min
% Baseline FVC	50% (nl 45–55)		

Fig. 32.2 Rate-responsive ventricular pacing with effective exercise performance. VVIR pacing using a standard piezoelectric crystal in an adolescent with idiopathic heart block who had an atrial lead fracture. While the heart rate response is mildly delayed, he reaches a peak heart rate of 150 beats per minute and with that achieves a $\dot{V}_{O2}$ max of 56 cc/kg/min with compensatory increase in his O2 pulse. Exercise blood pressure response is normal with no evidence of pacemaker syndrome. Despite the atrial lead failure, this programming change was sufficient to produce no subjective change and permit continued varsity level athletics

occurring in one in 15,000–20,000 live births, caused by injury to the fetal conduction system by placental transmission of maternal anti-SS-A/Ro and anti-SS-B/La antibodies [16]. The need for and timing of permanent pacemaker insertion in neonates and children with CCHB is dependent on age, escape rate, QRS duration, and the presence of symptoms attributable to bradycardia. Although children with unpaced CCHB compensate for their subnormal ventricular rates with augmented stroke volume and increased oxygen extraction, peak $\dot{V}_{O2}$ and peak work rates on average remain significantly lower than in age-matched normal subjects. The ventilatory anaerobic threshold (VAT) is depressed and reached sooner during exercise protocols than in healthy controls, providing further evidence of impaired tissue oxygenation [17]. Restoring chronotropic competence with dual-chamber pacing may not normalize exercise capacity, as the peak $\dot{V}_{O2}$ and anaerobic threshold remains depressed in clinically asymptomatic patients. Unlike their unpaced counterparts who augment stroke volume during exercise, CCHB patients with dual-chamber pacemakers do not increase their ventricular ejection fraction during exercise [18]. Adverse ventricular remodeling from chronic right ventricular pacing is seen in some of these patients (and may be subclinical in others). How much this can be improved with cardiac resynchronization therapy requires further study [19, 20].

In summary, even patients with isolated congenital or idiopathic complete heart block have different compensatory mechanism to exercise in native rhythm or when paced. They may have

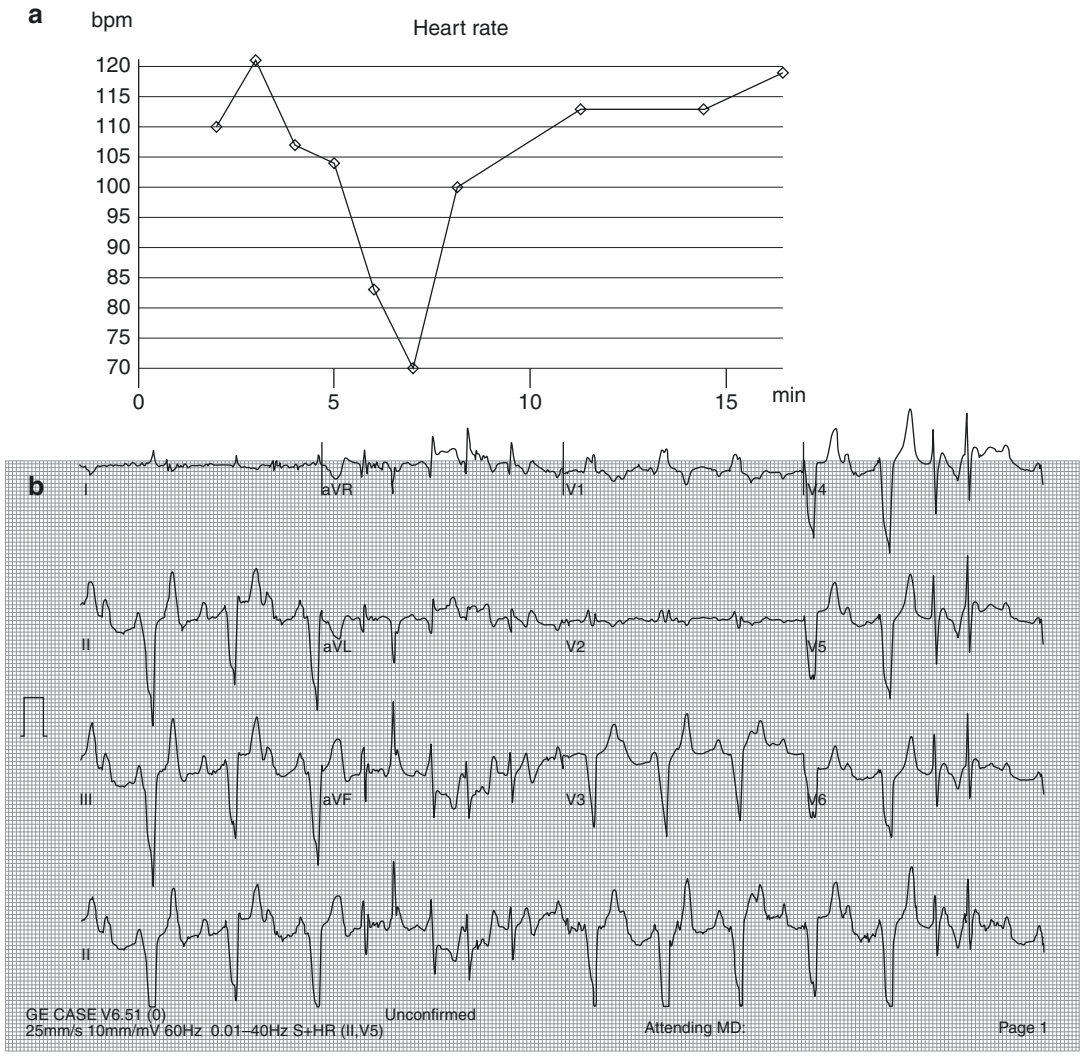


Fig. 32.3 Pacemaker-mediated 2:1 AV block in congenital heart disease. Dual-chamber pacing in a young adult with L-transposition, moderate-to-severe systemic atrioventricular valve insufficiency, and excessive sinus rate response to exercise. She has episodic atrial tachycardia and nonsustained ventricular tachycardia with one episode of ventricular fibrillation. The pacemaker rapidly develops pacemaker-mediated Wenckebach and then 2:1 block, which is demonstrated on the heart rate graph (**a**). While the mathematical analysis of her depressed exercise tolerance includes the substantial decrease in peak heart rate, her tolerance with this programming is comparable to a decade earlier when the upper rate was permitted to 150 beats per minute. The lower rate limit is programmed to 70 beats per minute to limit bradycardia during this high-rate behavior. (**b**) At peak exercise, she demonstrates a typical mix of 2:1 pacemaker-mediated block with untracked P waves both buried and visible within the QRST complex. In addition, there is complex ventricular or junctional ectopy above her lower rate limits and appropriately inhibiting pacing

concomitant chronotropic limitations that at times require rate-responsive pacing. All of these clinical issues are amplified in cardiomyopathy and structural heart disease. Exercise testing likely provides a useful tool for refining programming and clarifying exercise limitations. Upper rate response in dual-chamber pacing requires clinical judgment. For the patient with essentially normal anatomy and presumably low filling pressures, permitting paced rates up to 200 beats per minute

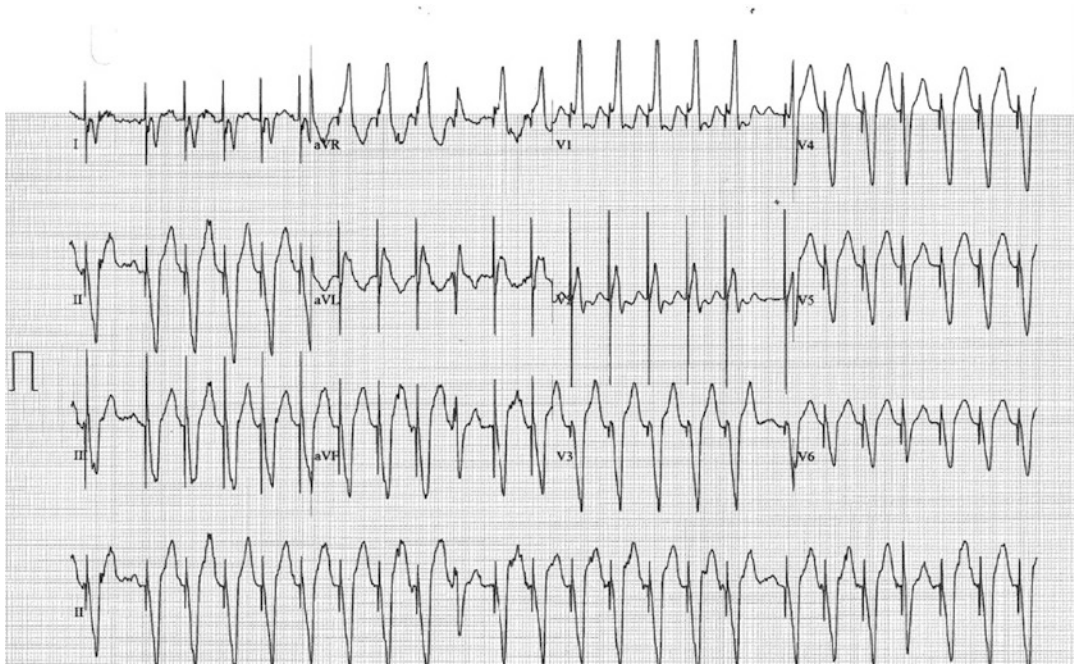


Fig. 32.4 Typical pacemaker-mediated Wenckebach with exercise: at 150 beats per minute with relatively typical high-rate behavior. There are some pauses from sinus beats that are not tracked and, in the middle of the tracing, an accelerated junctional or ventricular beat with a different QRS morphology

may well maximize exercise capacity. In contrast, combinations of restrictive physiology, AV valve stenosis, and ventricular dysfunction, particularly with known atrial arrhythmias, require lower upper rate limits to permit effective diastolic filling (Figs. 32.3a, b and 32.4).

Implantable Cardiac Defibrillators

Implantable cardiac defibrillators (ICDs) are used as primary or secondary prevention against unstable ventricular tachyarrhythmias in patients with structural heart disease, cardiomyopathy, or channelopathies. An effective ICD should only deliver a shock when a potentially life-threatening ventricular arrhythmia meets programmed detection criteria. While morphology discrimination algorithms exist, ICDs still struggle to differentiate between wide and narrow QRS complexes and thus are dependent on the absolute ventricular rate to discriminate ventricular from supraventricular and sinus tachycardia [21]. This limitation becomes especially pertinent in the pediatric population, because (1) sinus rates in children can exceed 200 beats per minute in the setting of extreme physical activity, agitation, and fever and (2) atrial tachycardias are highly prevalent in patients with repaired or palliated congenital heart disease. Moreover, the robust AV node conduction seen in normal children can allow for 1:1 AV transmission of sinus or nonsinus atrial tachycardias that would otherwise likely be blocked in adults. It is not surprising, therefore, that the frequency of inappropriate therapies (21%) in children with ICDs nears that of appropriate therapies (26%) [22]. In addition to earlier battery depletion and psychological consequences, inappropriate therapies have been associated with increased overall mortality in adult cohorts [23]. Attempts should be made not to overlap programmed detection rates with maximal sinus rates (which can be determined with formal exercise testing) or documented atrial tachycardia rates. If overlap cannot be avoided, exercise testing at least allows for informed, shared decision-making to occur between families and clinicians with regard to risk-benefit profiles of ongoing ICD use.

Practically, exercise testing with ICDs can be done safely with a clear set of precautions. The exercise physiologists and physicians need to know the parameters for therapy and terminate the test prior to reaching the VT therapy heart rate (typically stopping 20 beats per minute below the detection zone). The standard practice at Boston Children's Hospital is to interrogate the ICD prior to testing, to always perform exercise testing in ICD patients at the main campus, and to have a physician in the room to assist with supervision and, if needed, management. Exercise testing is a relatively routine part of the management of patients with ICD, with 90 of 244 patients with ICD followed at Boston Children's Hospital having had exercise testing during follow-up.

Evaluation of Tachycardia

Supraventricular Arrhythmias

Supraventricular tachycardia (SVT) is the most common arrhythmia in children. Due to its intermittent symptoms, assessment and documentation of the rhythm at time of symptoms can be difficult. For the patient with Wolf-Parkinson-White syndrome on EKG, there is a relatively clear management approach (see Chap. 31). For those with normal EKGs, the clinician and patient often need a variety of tools to clarify the diagnosis. Patients frequently report symptoms consistent with SVT during exercise. With exercise, there is an increase in circulating catecholamines associated with a decrease in parasympathetic tone, which leads to an increase in myocardial cell excitability and a decrease in the refractory period of the myocardium and His-Purkinje system. Those changes may make patients more vulnerable to supraventricular arrhythmias during exercise. However, EST has a poor sensitivity (0.1–19%) to diagnose SVT, even in patients with exertional symptoms [24–26]. Most episodes of SVT during exercise testing are short, self-resolving, asymptomatic, and only very rarely require intervention [24, 25]. When SVT occurs during exercise testing, the majority of patients have it during peak exercise, but up to one-third of patients will not demonstrate their tachycardia until recovery [24, 25].

All types of atrial arrhythmias can be seen during exercise testing. The distribution of mechanisms broadly reflects the age-expected findings, with atrioventricular reentry tachycardia and atrioventricular nodal reentry tachycardia more frequent in younger patients, while ectopic atrial tachycardia, atrial flutter, and atrial fibrillation are more frequent in older patients. The presence of artifact during exercise testing can make assessment of the mechanism of SVT difficult. The prevalence of atrial arrhythmias during exercise increases with age, suggesting a potential role for age-related increase in left atrial size and/or exaggerated catecholamine response to exercise. The presence of atrial arrhythmia during EST is not associated with exercise capacity or major adverse cardiac event during follow-up, but is associated with an increased risk of atrial arrhythmias during follow-up [25–27].

Ventricular Arrhythmias

Overview

Ventricular arrhythmias refer to arrhythmias originating from the ventricular myocardium and the His-Purkinje system. They can be hemodynamically stable, result in hemodynamic instability (presyncope, syncope, sudden cardiac arrest) or sudden cardiac death. The clinical presentation of these arrhythmias includes isolated ventricular ectopy, nonsustained ventricular tachycardia (NSVT) (3 or more consecutive ventricular complex lasting for less than 30 seconds and faster than age-based sinus rhythm), and sustained ventricular tachycardia (lasting for greater than 30 seconds or causing hemodynamic instability) [28]. Monomorphic ventricular arrhythmia refers to those with a single QRS morphology, while polymorphic ventricular arrhythmia refers to those with multiple QRS morphology. Monomorphic ventricular tachycardia (VT) can be further classified as outflow tract or idiopathic left ventricular VTs [29, 30]. Ventricular escape rhythms and minimally accelerated idioventricular rhythms occurring within resting

physiologic rates are not included in most discussions of clinically important ventricular ectopy; however, they need to be confidently recognized. There is no question that the classifications can shift over time and with additional data.

The spectrum, frequency, and prognosis of pediatric ventricular arrhythmias differ significantly between those with a structurally normal heart and among those with CHD, cardiomyopathy, and channelopathy [29]. Hence, evaluation and management of ventricular arrhythmia needs to be tailored based on the underlying myocardial substrate. While ventricular ectopy can be a common occurrence, sustained ventricular arrhythmias are relatively rare in the pediatric population even among those with congenital heart disease. However, sustained ventricular arrhythmias associated with either recognized or incompletely expressed CHD or cardiomyopathy can be directly correlated with the risk of sudden cardiac death. Assigning a short- or medium-term prognosis to ventricular arrhythmias can only be done after a full clinical evaluation.

Isolated Ventricular Ectopy

Premature ventricular contractions (PVCs) are common in children. About 10–50% of children with structurally normal hearts have PVCs during ambulatory monitoring, with higher frequency among neonates and adolescents [29, 31]. The frequency and complexity of those arrhythmias then increases steadily with maturity. Patients with known heart disease usually have a higher frequency of ectopy than those with structurally and functionally normal hearts. When evaluating ventricular ectopy in the exercise laboratory, a somewhat simplified approach is to classify it as incidentally identified ectopy in a test done for other indications, suppressed ventricular ectopy during exercise and exercise-induced ventricular ectopy.

There is ample experience that isolated ventricular (and atrial) ectopy is common during exercise testing. Our recent review identified isolated ventricular ectopy in 30% of studies. In a more pediatric-focused cohort, Ghosh reported exercise-induced arrhythmias in 28% of children [32]. In both series, clinically important arrhythmias were identified in less than 5% of patients. The overwhelming majority of data over the past decades support using criteria other than isolated ventricular ectopy to establish primary diagnoses and refine the risk of known heart disease. The clear exception to that is the identification of catecholaminergic ventricular tachycardia outlined later in this chapter.

In adults, increased PVCs during exercise testing, especially during the recovery period, are associated with increased all-cause and cardiovascular mortality [33]. That increase in risk is relatively small (odds ratios <2) and is observed over nearly a decade of follow-up. In young adults without symptoms, with a normal echocardiogram and ventricular ectopy that is suppressed on EST, there were no significant events over a 3–10-year follow-up period, and repeat testing showed a reduction in the arrhythmia burden [34]. When ventricular ectopy fails to suppress or increases with exercise, the risk of later cardiomyopathy appears to be increased; however, the frequency of this finding is widely variable. Suppression of ventricular ectopy with exercise testing has been suggested to be a marker of benign prognosis, although this has not been systematically evaluated in children [29]. The most recent systematic review suggests that more than 80% of children who undergo exercise testing for ventricular arrhythmias will have those suppressed at peak exercise [32]. Ventricular ectopy during childhood tends to regress when not associated with underlying cardiac disease; however, this might be less likely with PVCs of right ventricular origin [35].

While isolated ectopy has generally been viewed as a nuisance or essentially incidental finding, recent experience showing improved ventricular function after PVC ablation in patients with *both* decreased ventricular function and a high burden of isolated ectopy has raised the profile of frequent ectopy, *causing* cardiomyopathy. An ectopy burden of >10% and typically more than 20–30% is associated with left ventricular (LV) dysfunction in adults and has been suggested as a cut-off for further evaluation in children [29]. However, the risk of LV dysfunction in children with ventricular ectopy is more

convoluted with studies showing mixed results. While one of the studies demonstrated no risk of LV dysfunction with any degree of ectopy (monomorphic and polymorphic PVC, couplets, and nonsustained VT) in children with structurally normal hearts, another suggested that children with ectopy burden of approximately 50% and those with couplets had higher risk for LV dysfunction [36, 37]. The mixed data may reflect consequences of referral bias, with asymptomatic patients and lower ectopy burdens not being referred to centers with expertise in ablation. A reasonable conclusion is that patients demonstrating a modest burden, maybe >15–20% of their daily beats, warrant regular follow-up. In this setting the role of exercise testing is unclear. Stress echocardiogram may permit assessing left ventricular function without the confusion of variable loading conditions and the asynchrony of the PVCs.

Idiopathic Ventricular Tachycardias

Ventricular tachycardia is rare in childhood [38]. Outflow tract VTs account for the majority of the idiopathic VT in children and young adults. The underlying pathogenesis is triggered automaticity, usually in the right ventricular outflow tract, but can arise in the left ventricular outflow tract or the aortic cusps as well [29]. Patients typically present at around 5–8 years of age, with an incidental diagnosis, although up to a third of the patients can be symptomatic at presentation [39, 40]. Symptoms typically occur at rest or during the recovery period after exercise, with a small subset having exercise-induced symptoms. On evaluation, the ventricular ectopy typically has a left bundle branch block morphology with an inferior axis (Fig. 32.5). Practically, there is a continuum of presentations between isolated ventricular ectopy and more sustained runs of arrhythmia. Idiopathic left ventricular tachycardia

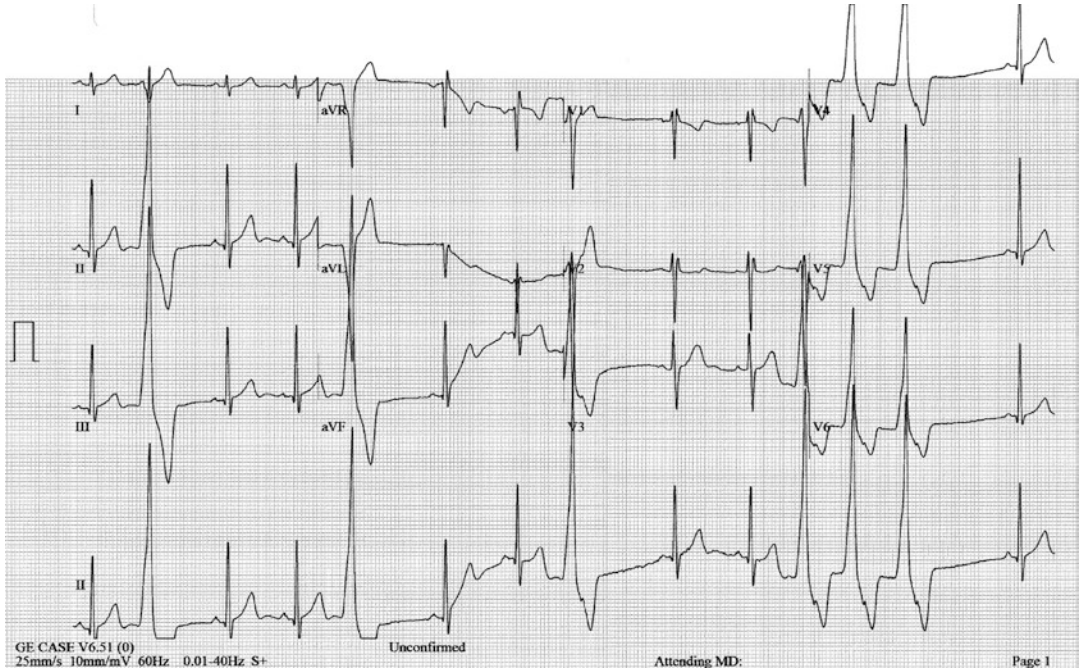


Fig. 32.5 Ectopy in outflow tract ventricular tachycardia. Repetitive ventricular ectopy and nonsustained VT with a left bundle branch block/inferior axis morphology supporting an outflow tract origin. The baseline EKG displays the VT morphology effectively in many leads. At peak exercise, this is completely suppressed with a normal EKG. Persistent symptoms of palpitations and arrhythmia density motivated an electrophysiology study with ablation in the left coronary cusp. The case study emphasizes the limitations of both EKG findings and exercise testing in correlating with subsequent clinical decision-making and the anatomic limitation of VT morphology analysis

(fascicular tachycardia), which may represent a microentrant circuit, is an alternative mechanism of sustained VT in normal hearts. Both practically and by definition, these syndromes are defined by the lack of underlying cardiac disease and a low suspicion of familial arrhythmia or cardiomyopathy syndromes.

While there are small older series reporting up to 50% ability to "reproduce" ventricular arrhythmias, those series were really conducted prior to modern classifications schemes and in >70% were reproducing nonsustained tachycardia that has previously been documented by other mechanisms. Exercise testing rarely induces sustained VT in children without established heart disease and even then rarely requires acute therapy [41, 42]. In one study of children with idiopathic VT, an equal number of patients had inducible VT and suppression of VT with exercise testing [39]. Most series demonstrate that the majority of patients have suppression of their arrhythmia on exercise testing [43]. The majority of the cases tend to have spontaneous resolution, especially among those with an early onset. Among patients requiring treatment, there is a good response to beta-blockers or calcium-channel blockers. Catheter ablation of outflow tract tachycardia can be done by activation or pace-mapping with reliable accuracy and limited complications [44]. Such ablations are typically reserved for symptomatic patients, those with ventricular dysfunction, and those who present with hemodynamically unstable VT.

Ventricular Arrhythmias in Congenital Heart Disease

As in patients without structural heart disease, ventricular ectopy and nonsustained VT are not rare among older patients with congenital heart disease. Sustained ventricular arrhythmias are relatively rare [45]. VT in patients with CHD can be classified as polymorphic (really myopathic ventricular arrhythmias) and scar-based macro-re-entrant tachycardia as in tetralogy of Fallot. The mortality risk may be higher in patients with polymorphic VT who frequently have substantial hemodynamic issues. ICDs should be strongly considered in this group of patients, with catheter ablation reserved for those with monomorphic tachycardia and as an adjunct to ICD placement. The primary role of exercise testing in most CHD is defining the overall exercise capacity with the arrhythmia and conduction disease an important, readily observed, additional data point in evaluating symptoms. This more modern formulation acknowledges that isolated or more complex ventricular ectopy may be seen during exercise testing, but keeps the focus on the overall hemodynamic function and specific arrhythmia symptoms.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia disorder characterized by recurrent episodes of atrial and ventricular arrhythmias during exercise or periods of stress [46]. Commonly presenting in late childhood, as many as 30% of patients will present with a cardiac arrest or aborted sudden cardiac death [47]. At baseline without provocation, there are no obvious electrocardiographic or echocardiographic abnormalities, often delaying the diagnosis. Family histories are also often negative as many mutations that cause CPVT are de novo without large family kindreds [48].

The clinical presentation often occurs in previously healthy individuals who experience atypical syncope during peak exercise or during strong emotional events. Evaluation with echocardiogram and baseline EKG will be normal. However, formal exercise testing will often reveal the presence of intermittent PVCs, couplets, triplets, and higher-order ectopy with increasing heart rate and exercise intensity. The presence of bidirectional ventricular tachycardia, although not occurring in all cases, is pathognomonic for CPVT and should immediately trigger an investigation for genetic causes of CPVT (Fig. 32.6a–d).

Over the last several years, genetic sequencing of individuals presenting with exercise or stress-induced arrhythmias has led to an increasingly complete picture of the genetic landscape of CPVT [48]. The vast majority of patients with CPVT (60–70%) will have a gain-of-function or loss-of-function mutations in the

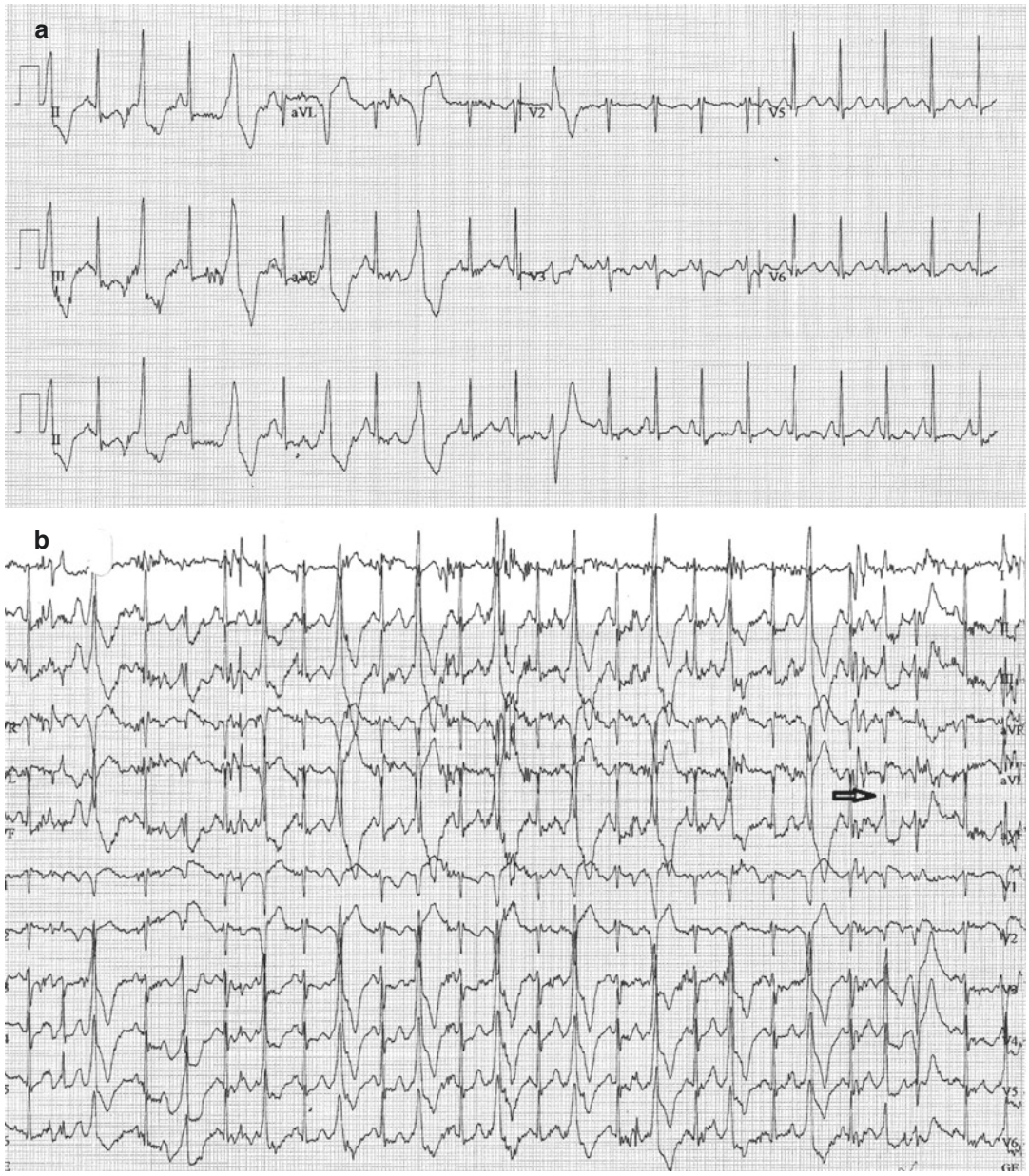


Fig. 32.6 Exercise testing in catecholaminergic ventricular tachycardia. Sequence of arrhythmia during an exercise test in an adolescent with RyR2-mediated catecholaminergic ventricular tachycardia (CPVT). (**a**) In early exercise with a heart rate of ~120 beats per minute, there is development of essentially monoform isolated ectopy, though some beats on the right side of the tracing display a second morphology. (**b**) At peak exercise, the overall arrhythmia density is increased, with examples of bidirectional couplets (arrow) and high-frequency baseline noise, which is typical in these tracings. (**c**) Early recovery with a transition to nearly monoform ventricular ectopy. (**d**) Late recovery, with the sinus rate back to essentially baseline where she continues with infrequent bidirectional ventricular couplets

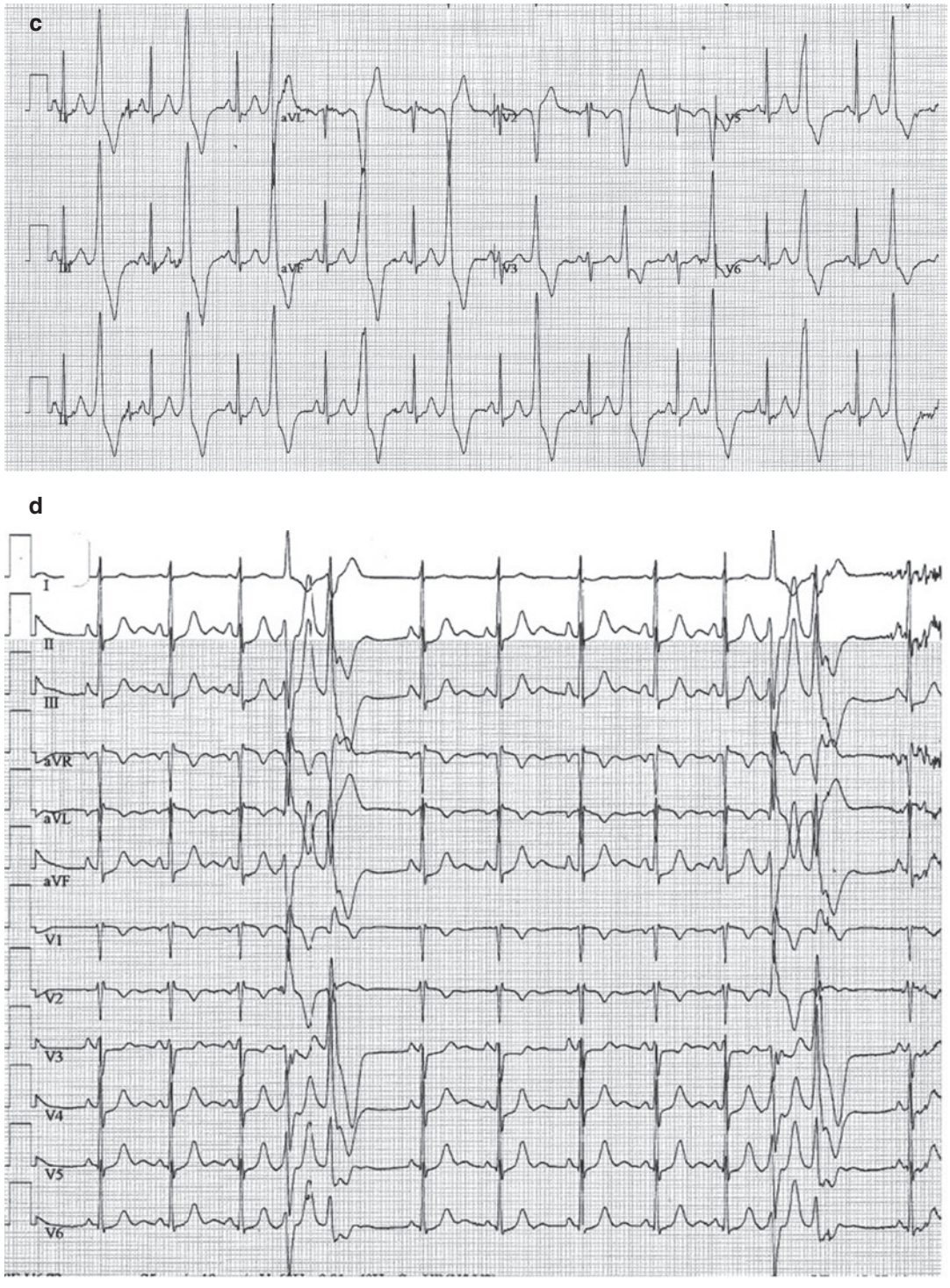


Fig. 32.6 (continued)

intracellular calcium release channel or ryanodine receptor 2 (RYR2). Interestingly, many of these mutations are de novo and are not present in related family members. While there are more than 160 reported mutations in the *RYR2* gene associated with CPVT, almost all occur in 4 canonical "hotspot" regions corresponding to protein interaction domains, areas for channel stability, or pore formation [49]. Several other forms of CPVT have been described, including homozygous loss of the sarcoplasmic reticulum calcium (Ca^{2+}) binding protein Calsequestrin 2 (*Casq2*), although this is rare and accounts for only 1–2% of clinical cases. Importantly, because many mutations are de novo and occur in probands without a positive family history for sudden death, there is often limited confirmatory information demonstrating pathogenicity for an individual mutation. Therefore, careful individualized patient phenotyping is critical to establish causation of mutations obtained through clinical genetics.

EST for patients suspected to carry the diagnosis of CPVT remains a mainstay for establishing the diagnosis. It is especially true for any patient that presents with atypical syncope or cardiac arrest during exercise without a structural or functional abnormality. While exercise stress testing can demonstrate abnormalities including PVCs, couplets, bidirectional triplets, nonsustained VT, and even atrial tachycardias, there is no established criterion for what constitutes a positive test. In an effort to establish the sensitivity and specificity of EST for the diagnosis of CPVT, Hayashi and colleagues [50] examined a cohort of asymptomatic family members of 17 CPVT probands. Using the presence of PVCs, couplets, or nonsustained VT in previously asymptomatic individuals established the diagnosis in 16 of 17 relatives subsequently confirmed by genetic diagnosis, giving a specificity of 94%. However, the sensitivity was only 50% in the same cohort after genetic confirmation and subsequent follow-up, demonstrating clinical tachycardia. Therefore, serial EST may be necessary to establish a diagnosis and is recommended when the clinical suspicion for CPVT is sufficiently elevated.

The typical presentation of arrhythmia during exercise testing in CPVT patients is often progressive escalation of ectopy starting with single PVCs, followed by couplets and even salvos of NSVT as the heart rate increases. Ventricular ectopy in CPVT stereotypically occurs as the patient's heart rate approaches between 100 and 120 beats per minute. As exercise intensity increases, single PVCs can increase in frequency and commonly will occur in a bigeminal pattern. Both monomorphic and polymorphic ectopies are commonplace, with some patients demonstrating an atrial phenotype with frequent bursts of atrial ectopy and atrial tachycardia. Upon cessation of exercise, the presence of ectopy, regardless of severity and frequency, resolves immediately without any significant arrhythmia in recovery. In addition to establishing a diagnosis of CPVT, serial exercise stress testing has become invaluable in long-term follow-up and management of patients with CPVT [51]. This is particularly important with initiation of antiarrhythmics, such as flecainide, where the minimal effective dose is selected by demonstration of arrhythmia suppression after achieving steady-state drug levels (Fig. 32.7).

Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy is an important cause of exertional sudden death in otherwise healthy young individuals. Children can be referred for evaluation of arrhythmogenic cardiomyopathy due to the presence of exertional palpitation or syncope, EKG abnormalities (T wave inversion), PVC, ventricular tachycardia, family history of arrhythmogenic cardiomyopathy, and/or sudden cardiac death. Diagnosis can be challenging, especially in young children, and is based on the task force diagnostic criteria for arrhythmogenic cardiomyopathy [52]. EST is often used in the evaluation of those patients, despite limited evidence of its utility in the diagnosis of patients with arrhythmogenic cardiomyopathy. Almost all patients with arrhythmogenic cardiomyopathy and a history of sustained ventricular tachycardia or cardiac arrest have PVCs

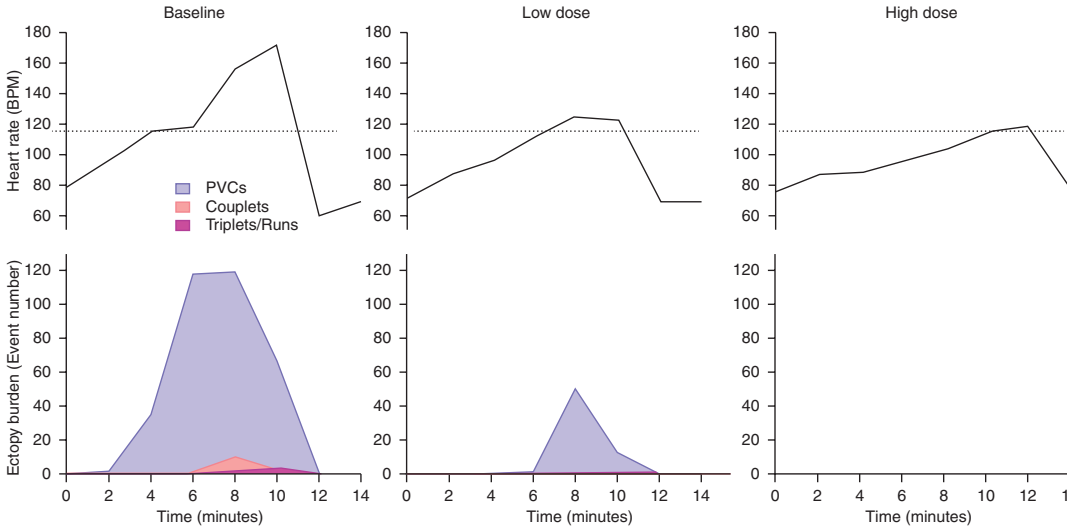


Fig. 32.7 Serial exercise testing for monitoring of therapy in CPVT. A 9-year-old female with a pathogenic RyR2 mutation (RYR@-G3946S) and a history of recurrent ventricular tachycardias with syncope was admitted to the hospital for initiation of flecainide. The far left panel demonstrates frequent ventricular ectopy during her baseline exercise stress test on high-dose nadolol, prior to flecainide initiation. The middle panel shows a significant reduction in ectopy on low-dose flecainide (50 mg BID), which is nearly entirely suppressed on high-dose (100 mg BID) flecainide. Note the decrease in maximal heart rate with increasing flecainide dosing despite similar efforts on each exercise test

during exercise testing (92%) [53]; however, that number is much lower in patients without a history of sustained arrhythmia (61%) [54]. Similarly, approximately half of asymptomatic gene carriers who do not meet task force criteria for arrhythmogenic cardiomyopathy have PVCs during exercise testing [53]. PVCs with a superior axis may be more specific for arrhythmogenic cardiomyopathy and are not usually seen in healthy controls [53]. In most patients, PVCs and ventricular arrhythmia occur at peak exercise, or immediately during post-exercise recovery [54, 55]. However, the presence of PVCs or higher-grade ventricular arrhythmia during exercise testing is very variable, and not reproducible on follow-up exercise testing [54]. Also, a significant proportion of patients with arrhythmogenic cardiomyopathy have suppression of PVCs at peak exercise, making distinction between arrhythmogenic cardiomyopathy and benign ventricular ectopy difficult (Fig. 32.8a, b) [55]. Other anomalies occasionally seen in patients with arrhythmogenic cardiomyopathy during exercise include new epsilon waves (14%) and prolonged QRS terminal activation duration (32%). New T wave inversion or ST-segment elevation during exercise testing is not specific for arrhythmogenic cardiomyopathy, and seen in a similar proportion of healthy controls [53]. Moreover, the presence of arrhythmia on exercise testing is not predictive of the risk of ventricular arrhythmia on follow-up [54]. Thus, caution should be applied in the interpretation of exercise stress test in patients with a suspicion of arrhythmogenic cardiomyopathy due to the wide variation of findings, and a normal exercise test should not be considered reassuring, especially in young children.

T-Wave Alternans

T-wave alternans visible on surface EKG is a hallmark of severe prolonged QT syndrome. Microvolt T-wave alternans (MTWA) is the finding of microvolt level oscillations in the T-wave amplitude and represents a strong univariate predictor of ventricular arrhythmias in adults [56]. Several software techniques have been developed that permit assessment of T-wave alternans with

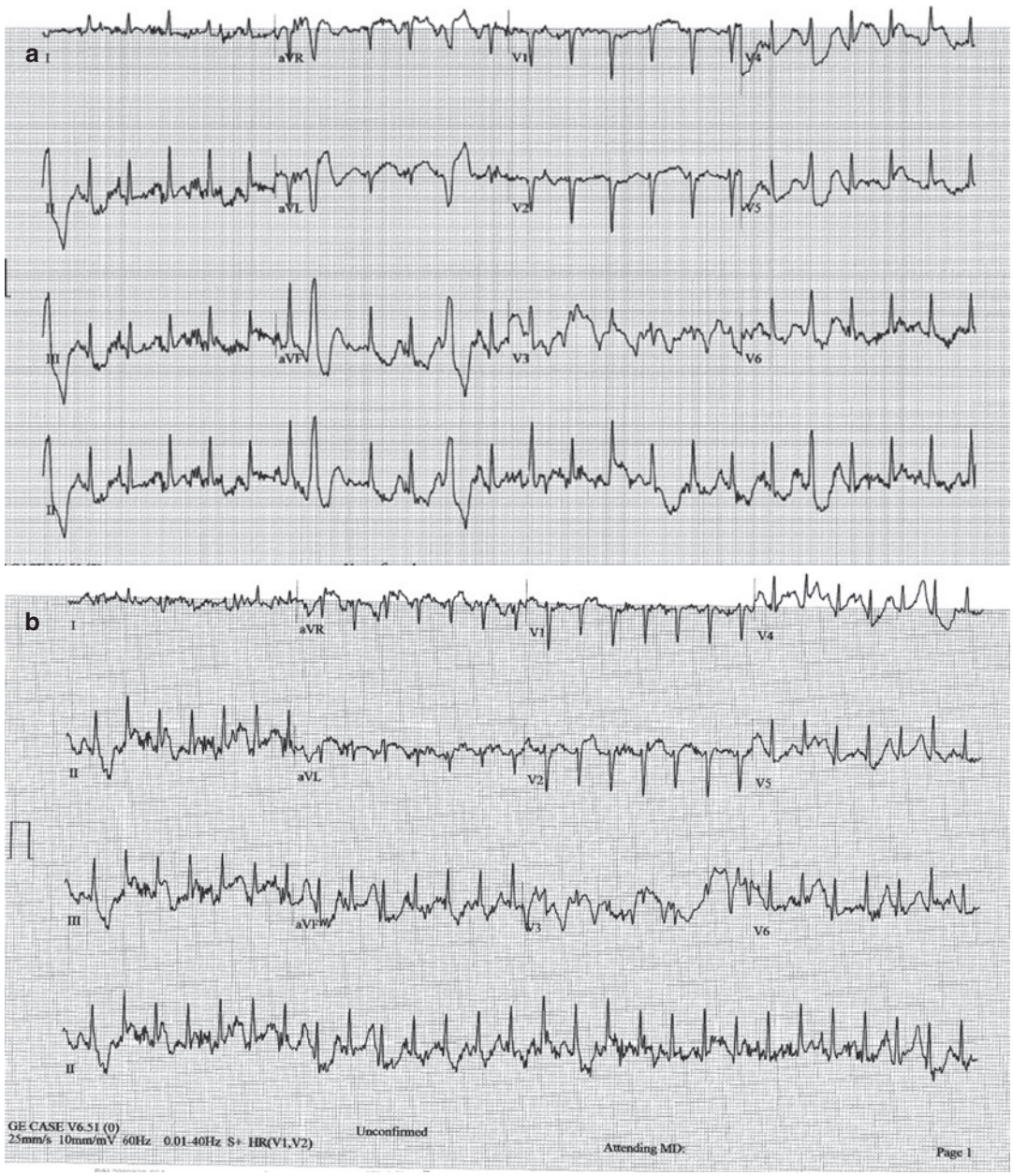


Fig. 32.8 Exercise testing in arrhythmogenic cardiomyopathies. Exercise test in the 14-year-old daughter of a parent with clinical arrhythmogenic cardiomyopathy who had mid exertional syncope. She had normal EKG, echocardiogram, and MRI, and, at the time, there was no genetic marker. Subsequent evaluation demonstrated a PKP2 mutation in both. (**a**) With mid exercise, there is complex ectopy with couplets and fused beats, probably with a later precordial transition than the pattern seen in Fig. 32.4. With peak exercise, this was suppressed. (**b**) Subsequent course was notable for increased phenotypic expression including sustained monomorphic VT on implantable loop recording

exercise. Pediatric data are limited, but MTWA is seen in only 11% of normal children though not at heart rates <120 beats per minute [57]. In adolescents with repaired tetralogy of Fallot, MWTA is reliably identified in a higher percentage (23%) of patients and at lower heart rates. However, in this group of patients with a low risk of life-threatening arrhythmias, MWTA had no predictive value [58]. Early-onset MWTA was shown to be a predictor of ventricular arrhythmias in patients with CHD, cardiomyopathy, myocardial ischemia, syncope, or cardiac arrest. When we examined the Boston Children's Hospital experience, we demonstrated early onset in 7% of a relatively high-risk heterogeneous cohort. While the relative risk associated with early-onset MWTA was 8.1, the overall positive predictive values ranged from 58% to 82% for ventricular arrhythmia or a "high-risk" clinical situation. The negative predictive value was high, ranging from 94% for cardiac arrest to 81% for ventricular arrhythmia. However, including MWTA in an analysis of traditional risk factors added little information [59]. Based on this analysis, while some groups have continued to collect MWTA regularly as part of exercise testing, Boston Children's Hospital has abandoned this test in favor of an evolving risk formulation that focuses on arrhythmia symptoms, underlying disease, and ventricular function. This analysis mirrors a number of observations in the adolescent and young adults with CHD or arrhythmia where the overall incidence of life-threatening complications is relatively low and predictive tools are often quite limited.

Conclusion

- Exercise testing is a routine part of the assessment of many forms of heart disease. EST-related arrhythmia data must be interpreted in the context of the high incidence of clinically unimportant, low-grade atrial and ventricular ectopy that may be encountered during EST. Comprehensive assessment of patients with AVB and pacemakers using EST, including expired gas analysis when feasible, can help define their functional capacity and inform decision-making about programming, lead revisions, or deferring therapy.
- While atrial and ventricular arrhythmias are commonly seen with EST, these are almost always nonsustained [41] and the significance of those findings is, at best, modest. Most decision-making focuses on symptoms and underlying disease.
- Exercise testing has variable roles in the evaluation of ventricular arrhythmias.
  - For patients with structurally normal hearts and combinations of isolated and repetitive ventricular ectopy, EST offers some mechanistic data and some marginal long-term prognostic data.
    - Patients with increased ectopy during exercise or immediately post-exercise deserve enhanced follow-up.
    - Decisions about therapy are primarily focused on symptoms and the presence of ventricular dysfunction [29, 30].
  - Catecholaminergic polymorphic VT is a specific genetic and clinical disorder that is defined by the exercise arrhythmia response. Repeated EST is one part of sequential assessment of therapy.
  - For arrhythmogenic cardiomyopathies, while exercise testing is part of their overall clinical and phenotypic characterization, the response to EST will generally be only part of the overall decision-making.
- For SVT and sustained atrial or ventricular arrhythmias in patients with CHD, there are little additional arrhythmia data that EST offers.
  - In CHD, exercise testing is primarily helpful in assessing the overall risk profile of patients. Focusing on the hemodynamic and the associated disease-specific risks for ventricular arrhythmias is appropriate.
- Exercise testing can help refine both ICD programming and medical therapy to limit inappropriate and appropriate therapies.

References

1. Flinn CJ, Wolff GS, Dick M, Campbell RM, Borkat G, Casta A, et al. Cardiac rhythm after the Mustard operation for complete transposition of the great arteries. N Engl J Med. 1984;310(25):1635–8.
2. Dos L, Teruel L, Ferreira IJ, Rodriguez-Larrea J, Miro L, Girona J, et al. Late outcome of Senning and Mustard procedures for correction of transposition of the great arteries. Heart. 2005;91(5):652–6.
3. Douard H, Labbé L, Barat JL, Broustet JP, Baudet E, Choussat A. Cardiorespiratory response to exercise after venous switch operation for transposition of the great arteries. Chest. 1997;111(1):23–9.
4. Fredriksen PM, Pettersen E, Thaulow E. Declining aerobic capacity of patients with arterial and atrial switch procedures. Pediatr Cardiol. 2009;30(2):166–71.
5. Petko M, Myung RJ, Wernovsky G, Cohen MI, Rychik J, Nicolson SC, et al. Surgical reinterventions following the Fontan procedure. Eur J Cardiothorac Surg. 2003;24(2):255–9.
6. Fishberger SB, Wernovsky G, Gentles TL, Gamble WJ, Gauvreau K, Burnett J, et al. Long-term outcome in patients with pacemakers following the Fontan operation. Am J Cardiol. 1996;77(10):887–9.
7. Attenhofer Jost CH, Connolly HM, Danielson GK, Bailey KR, Schaff HV, Shen WK, et al. Sinus venosus atrial septal defect: long-term postoperative outcome for 115 patients. Circulation. 2005;112(13):1953–8.
8. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61(3):e6–75.
9. den Dulk K, Lindemans FW, Brugada P, Smeets JL, Wellens HJ. Pacemaker syndrome with AAI rate variable pacing: importance of atrioventricular conduction properties, medication, and pacemaker programmability. Pacing Clin Electrophysiol. 1988;11(8):1226–33.
10. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, Goldschlager NF, Hamilton RM, Joglar JA, Kim RJ, Lee R, Marine JE, McLeod CJ, Oken KR, Patton KK, Pellegrini CN, Selzman KA, Thompson A, Varosy PD. 2018. ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. Heart Rhythm. 2018. pii: S1547-5271(18)31127-5. https://doi.org/10.1016/j.hrthm.2018.10.037.
11. Schüller H, Brandt J. The pacemaker syndrome: old and new causes. Clin Cardiol. 1991;14(4):336–40.
12. Alpert MA, Curtis JJ, Sanfelippo JF, Flaker GC, Walls JT, Mukerji V, et al. Comparative survival after permanent ventricular and dual chamber pacing for patients with chronic high degree atrioventricular block with and without preexistent congestive heart failure. J Am Coll Cardiol. 1986;7(4):925–32.
13. Menozzi C, Brignole M, Moracchini PV, Lolli G, Bacchi M, Tesorieri MC, et al. Intrapatient comparison between chronic VVIR and DDD pacing in patients affected by high degree AV block without heart failure. Pacing Clin Electrophysiol. 1990;13(12 Pt 2):1816–22.
14. Hargreaves MR, Channon KM, Cripps TR, Gardner M, Ormerod OJ. Comparison of dual chamber and ventricular rate responsive pacing in patients over 75 with complete heart block. Br Heart J. 1995;74(4):397–402.
15. Oldroyd KG, Rae AP, Carter R, Wingate C, Cobbe SM. Double blind crossover comparison of the effects of dual chamber pacing (DDD) and ventricular rate adaptive (VVIR) pacing on neuroendocrine variables, exercise performance, and symptoms in complete heart block. Br Heart J. 1991;65(4):188–93.
16. Michaëlsson M, Engle MA. Congenital complete heart block: an international study of the natural history. Cardiovasc Clin. 1972;4(3):85–101.
17. Reybrouck T, Vanden Eynde B, Dumoulin M, Van der Hauwaert LG. Cardiorespiratory response to exercise in congenital complete atrioventricular block. Am J Cardiol. 1989;64(14):896–9.
18. Motonaga KS, Punn R, Axelrod DM, Ceresnak SR, Hanisch D, Kazmucha JA, et al. Diminished exercise capacity and chronotropic incompetence in pediatric patients with congenital complete heart block and chronic right ventricular pacing. Heart Rhythm. 2015;12(3):560–5.
19. Thambo JB, Bordachar P, Garrigue S, Lafitte S, Sanders P, Reuter S, et al. Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. Circulation. 2004;110(25):3766–72.
20. Karpawich PP, Rabah R, Haas JE. Altered cardiac histology following apical right ventricular pacing in patients with congenital atrioventricular block. Pacing Clin Electrophysiol. 1999;22(9):1372–7.
21. Koneru JN, Swerdlow CD, Wood MA, Ellenbogen KA. Minimizing inappropriate or "unnecessary" implantable cardioverter-defibrillator shocks: appropriate programming. Circ Arrhythm Electrophysiol. 2011;4(5):778–90.
22. Stephenson EA, Batra AS, Knilans TK, Gow RM, Gradaus R, Balaji S, et al. A multicenter experience with novel implantable cardioverter defibrillator configurations in the pediatric and congenital heart disease population. J Cardiovasc Electrophysiol. 2006;17(1):41–6.
23. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med. 2012;367(24):2275–83.
24. Draper DE, Giddins NG, McCort J, Gross GJ. Diagnostic usefulness of graded exercise testing in pediatric supraventricular tachycardia. Can J Cardiol. 2009;25(7):407–10.

25. Maurer MS, Shefrin EA, Fleg JL. Prevalence and prognostic significance of exercise-induced supraventricular tachycardia in apparently healthy volunteers. Am J Cardiol. 1995;75(12):788–92.
26. Bhat DP, Du W, Karpawich PP. Testing efficacy in determination of recurrent supraventricular tachycardia among subjectively symptomatic children following "successful" ablation. Pacing Clin Electrophysiol. 2014;37(8):1009–16.
27. Bunch TJ, Chandrasekaran K, Gersh BJ, Hammill SC, Hodge DO, Khan AH, et al. The prognostic significance of exercise-induced atrial arrhythmias. J Am Coll Cardiol. 2004;43(7):1236–40.
28. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association task force and the European Society of Cardiology Committee for practice guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114(10):e385–484.
29. Crosson JE, Callans DJ, Bradley DJ, Dubin A, Epstein M, Etheridge S, et al. PACES/HRS expert consensus statement on the evaluation and management of ventricular arrhythmias in the child with a structurally normal heart. Heart Rhythm. 2014;11(9):e55–78.
30. Pedersen CT, Kay GN, Kalman J, Borggrefe M, Della-Bella P, Dickfeld T, et al. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. Heart Rhythm. 2014;11(10):e166–96.
31. Cohen MI. Frequent premature ventricular beats in healthy children: when to ignore and when to treat? Curr Opin Cardiol. 2019;34(1):65–72. https://doi.org/10.1097/HCO.0000000000000581.
32. Ghosh RM, Gates GJ, Walsh CA, Schiller MS, Pass RH, Ceresnak SR. The prevalence of arrhythmias, predictors for arrhythmias, and safety of exercise stress testing in children. Pediatr Cardiol. 2015;36(3):584–90.
33. Kim J, Kwon M, Chang J, Harris D, Gerson MC, Hwang SS, et al. Meta-analysis of prognostic implications of exercise-induced ventricular premature complexes in the general population. Am J Cardiol. 2016;118(5):725–32.
34. Verdile L, Maron BJ, Pelliccia A, Spataro A, Santini M, Biffi A. Clinical significance of exercise-induced ventricular tachyarrhythmias in trained athletes without cardiovascular abnormalities. Heart Rhythm. 2015;12(1):78–85.
35. Beaufort-Krol GC, Dijkstra SS, Bink-Boelkens MT. Natural history of ventricular premature contractions in children with a structurally normal heart: does origin matter? Europace. 2008;10(8):998–1003.
36. Bertels RA, Harteveld LM, Filippini LH, Clur SA, Blom NA. Left ventricular dysfunction is associated with frequent premature ventricular complexes and asymptomatic ventricular tachycardia in children. Europace. 2017;19(4):617–21.
37. Guerrier K, Anderson JB, Czosek RJ, Mays WA, Statile C, Knilans TK, et al. Usefulness of ventricular premature complexes in asymptomatic patients ≤21 years as predictors of poor left ventricular function. Am J Cardiol. 2015;115(5):652–5.
38. Roggen A, Pavlovic M, Pfammatter JP. Frequency of spontaneous ventricular tachycardia in a pediatric population. Am J Cardiol. 2008;101(6):852–4.
39. Harris KC, Potts JE, Fournier A, Gross GJ, Kantoch MJ, Cote JM, et al. Right ventricular outflow tract tachycardia in children. J Pediatr. 2006;149(6):822–6.
40. Pfammatter JP, Paul T. Idiopathic ventricular tachycardia in infancy and childhood: a multicenter study on clinical profile and outcome. Working Group on Dysrhythmias and Electrophysiology of the Association for European Pediatric Cardiology. J Am Coll Cardiol. 1999;33(7):2067–72.
41. Barry OM, Gauvreau K, Rhodes J, Reichman JR, Bourette L, Curran T, et al. Incidence and predictors of clinically important and dangerous arrhythmias during exercise tests in pediatric and congenital heart disease patients. JACC Clin Electrophysiol. 2018;4(10):1319–27.
42. Bricker JT, Traweek MS, Smith RT, Moak JP, Vargo TA, Garson A Jr. Exercise-related ventricular tachycardia in children. Am Heart J. 1986;112(1):186–8.
43. Song MK, Baek JS, Kwon BS, Kim GB, Bae EJ, Noh CI, et al. Clinical spectrum and prognostic factors of pediatric ventricular tachycardia. Circ J. 2010;74(9):1951–8.
44. Morwood JG, Triedman JK, Berul CI, Khairy P, Alexander ME, Cecchin F, et al. Radiofrequency catheter ablation of ventricular tachycardia in children and young adults with congenital heart disease. Heart Rhythm. 2004;1(3):301–8.
45. Khairy P, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, et al. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). Can J Cardiol. 2014;30(10):e1–e63.
46. Napolitano C, Bloise R, Memmi M, Priori SG. Clinical utility gene card for: catecholaminergic polymorphic ventricular tachycardia (CPVT). Eur J Hum Genet. 2014;22(1). https://doi.org/10.1038/ejhg.2013.55.
47. Napolitano C, Bloise R, Monteforte N, Priori SG. Sudden cardiac death and genetic ion channelopathies: long QT, Brugada, short QT, catecholaminergic polymorphic ventricular tachycardia,

and idiopathic ventricular fibrillation. Circulation. 2012;125(16):2027–34.
48. Sumitomo N. Current topics in catecholaminergic polymorphic ventricular tachycardia. J Arrhythm. 2016;32(5):344–51.
49. Campuzano O, Beltran-Alvarez P, Iglesias A, Scornik F, Perez G, Brugada R. Genetics and cardiac channelopathies. Genet Med. 2010;12(5):260–7.
50. Hayashi M, Denjoy I, Hayashi M, Extramiana F, Maltret A, Roux-Buisson N, et al. The role of stress test for predicting genetic mutations and future cardiac events in asymptomatic relatives of catecholaminergic polymorphic ventricular tachycardia probands. Europace. 2012;14(9):1344–51.
51. Kannankeril PJ, Moore JP, Cerrone M, Priori SG, Kertesz NJ, Ro PS, et al. Efficacy of flecainide in the treatment of catecholaminergic polymorphic ventricular tachycardia: a randomized clinical trial. JAMA Cardiol. 2017;2(7):759–66.
52. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation. 2010;121(13):1533–41.
53. Perrin MJ, Angaran P, Laksman Z, Zhang H, Porepa LF, Rutberg J, et al. Exercise testing in asymptomatic gene carriers exposes a latent electrical substrate of arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol. 2013;62(19):1772–9.
54. Karlsson D, Engvall J, Ando AA, Aneq MA. Exercise testing for long-term follow-up in arrhythmogenic right ventricular cardiomyopathy. J Electrocardiol. 2017;50(2):176–83.
55. Sequeira IB, Kirsh JA, Hamilton RM, Russell JL, Gross GJ. Utility of exercise testing in children and teenagers with arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol. 2009;104(3):411–3.
56. Verrier RL, Klingenheben T, Malik M, El-Sherif N, Exner DV, Hohnloser SH, et al. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility – consensus guideline by International Society for Holter and Noninvasive Electrocardiology. J Am Coll Cardiol. 2011;58(13):1309–24.
57. Cheung MM, Davis AM, Cohen RJ, Wilkinson JL. T wave alternans threshold in normal children. J Cardiovasc Electrophysiol. 2001;12(4):424–7.
58. Cheung MM, Weintraub RG, Cohen RJ, Karl TR, Wilkinson JL, Davis AMCRJ. T wave alternans threshold late after repair of tetralogy of Fallot. J Cardiovasc Electrophysiol. 2002;13(7):657–61.
59. Alexander ME, Cecchin F, Huang KP, Berul CI. Microvolt t-wave alternans with exercise in pediatrics and congenital heart disease: limitations and predictive value. Pacing Clin Electrophysiol. 2006;29(7):733–41.

Part VI

Interesting/Instructive Cases

An illustrious endocrinologist is alleged to have said, “Don’t tell me if the calcium is high or low, I can explain it either way!”. Similarly, data from exercise tests may be open to multiple, valid interpretations. Indeed, the exchange of ideas that accompanies the analysis and interpretation of these tests constitutes one of the most appealing features of our discipline. In this section, we will present data drawn from a number of interesting and informative cases. We will provide our interpretation of the data, but recognize that others may have different interpretations and reach different conclusions.

33 Patients with Physiologically Normal Hearts and Lungs

Jonathan Rhodes

Case 33.1: "Fatigue" (Normal Study)

This was an 11-year-old girl who was referred for cardiologic evaluation on account of fatigue. She was diagnosed with mononucleosis about a year prior to her cardiologic evaluation. She experienced extreme fatigue during that illness and continued to experience some fatigue in the months thereafter. Her family had consulted with a sports medicine physician, who had recommended an exercise regimen. Despite increasing her level of physical activity, she and her family continued to feel that her ability to exercise was impaired. She had been to specialists in otolaryngology, pulmonology, and sleep medicine, without a diagnosis. She had also consulted with a pediatric cardiologist who detected no abnormalities on physical examination or on echocardiography. She came to Boston Children's Hospital for a second opinion. A cardiopulmonary exercise test (CPET) was obtained to further assess her symptoms.

The CPET was performed on a cycle ergometer with a 12 W/min ramp (Fig. 33.1 and Table 33.1). She achieved a peak respiratory exchange ratio (RER) of 1.14, indicating that she expended an adequate effort. Her peak $\dot{V}_{O2}$, work rate, oxygen pulse, and heart rate were normal. Her $\dot{V}_{O2}$ at the ventilatory anaerobic threshold (VAT) was also normal. She had an ample breathing reserve at peak exercise. Her baseline spirometry and gas exchange during exercise were normal. No arrhythmias or STT changes were detected during the study. Her blood pressure response to exercise was normal. Exercise was terminated on account of "leg fatigue." In short, the CPET was completely normal.

The patient and her family appeared to be reassured by the results of the CPET and no longer sought consultations from subspecialists.

This case illustrates the fact that a child's (and/or the child's family's) perception of his/her exercise function may be unreliable [1]. Under these circumstances, objectively assessing the child's exercise function can be enlightening and, when normal, enormously reassuring to the patient and/or the family. Indeed, in some cases an exercise test can be both diagnostic and therapeutic!

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_33

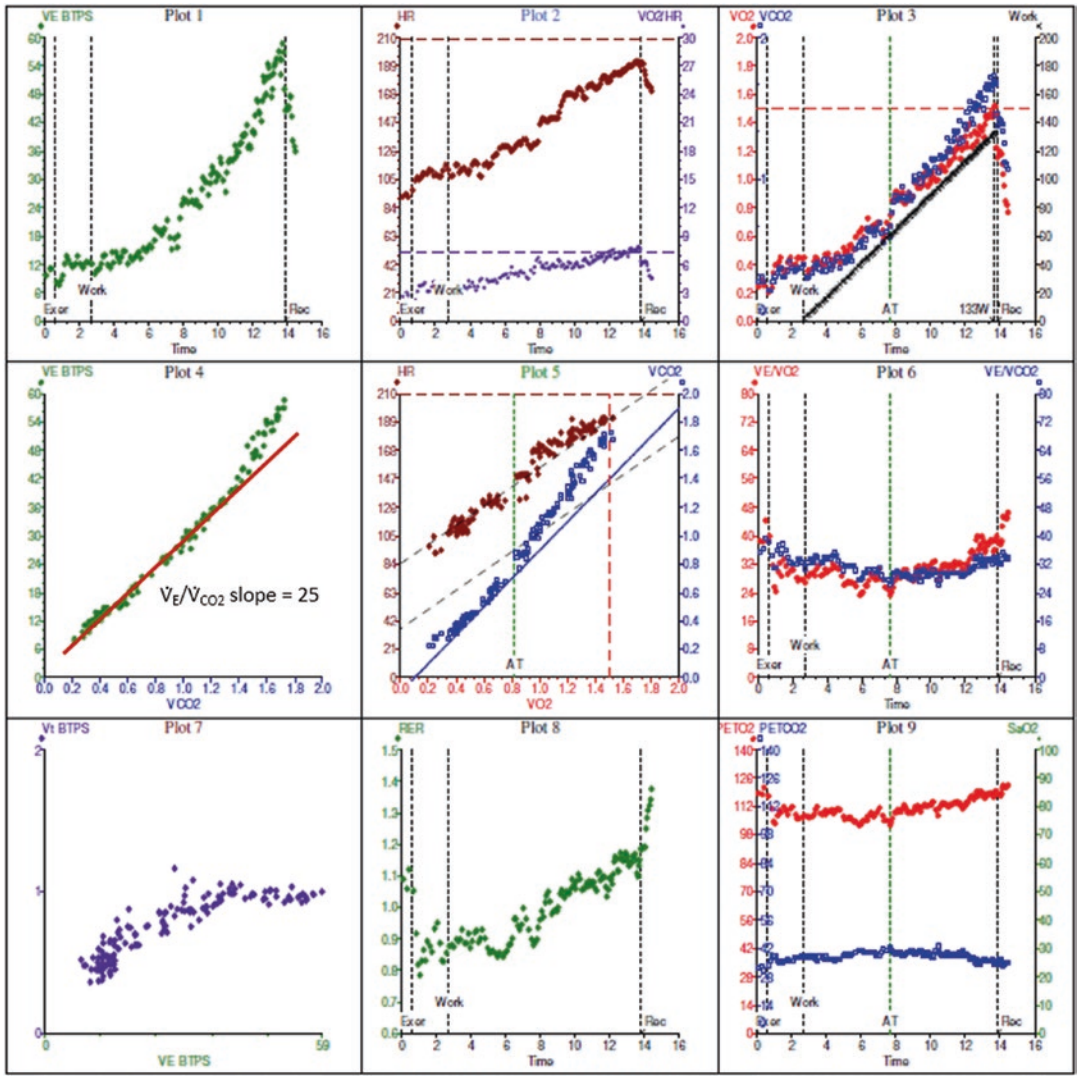


Fig. 33.1 Nine-panel graph of data from cardiopulmonary exercise test from patient 33.1: fatigue (normal study). Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, PETCO2 end-tidal pCO2, PETO2 end-tidal pO2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, $\dot{V}_{O2}$ oxygen consumption, $\dot{V}_{O2}$/HR oxygen pulse

Table 33.1 Patient 33.1. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	44.0
Peak $\dot{V}_{O2}$ (%predicted)	102
Peak work rate (W)	133
Peak work rate (%predicted)	118
Peak RER	1.14
Peak O_2 pulse (%predicted)	104
Peak heart rate (bpm)	190
Peak heart rate (%predicted)	98
Heart rate increase	Normal
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	49
End-tidal pCO_2 at VAT (mm Hg)	39
End-tidal pCO_2 during exercise	Normal
$\dot{V}_E/\dot{V}_{CO2}$ slope	25
Forced vital capacity (%predicted)	88
FEV1 (%predicted)	99
FEF 25–75 (%predicted)	92
Breathing reserve (%)	38
Rhythm	Sinus rhythm throughout study
Blood pressure response	Normal
Oxygen saturation at rest (%)	98
Oxygen saturation at peak exercise (%)	97

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold, *FEV1* volume exhaled in the first second of forced expiration, *FEF* forced expiratory flow

Case 33.2: Anxiety-Related Hyperventilation

The patient was an 8-year-old boy who was status post of a coarctation of the aorta and subsequent modified Konno procedure for subaortic stenosis. He had an excellent result from these procedures, with only mild residual aortic stenosis, no arch obstruction, and normal ventricular function. He was asymptomatic. He was referred for a CPET to further assess his current cardiopulmonary status.

He performed the exercise test on a cycle ergometer with a 10 W/min ramp (Table 33.2 and Fig. 33.2). His peak RER was 1.12, indicating that he expended a good effort. His peak work rate and peak $\dot{V}_{O2}$ were normal. His peak heart rate was slightly low (84% predicted), suggesting

Table 33.2 Patient 33.2: anxiety-related hyperventilation. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	44.9
Peak $\dot{V}_{O2}$ (%predicted)	110
Peak work rate (W)	63
Peak work rate (%predicted)	89
Peak RER	1.12
Peak O_2 pulse (%predicted)	131
Peak heart rate (bpm)	164
Peak heart rate (%predicted)	84
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	53
End-tidal pCO_2 at VAT (mm Hg)	36
End-tidal pCO_2 during exercise	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	39
Forced vital capacity (%predicted)	102
FEV1 (%predicted)	97
FEF 25–75 (%predicted)	85
Breathing reserve (%)	37
Rhythm	Sinus rhythm throughout study
Blood pressure response	Normal

that mild sinus node dysfunction may have been present. However, he was able to compensate for this chronotropic defect by increasing his oxygen pulse to supranormal levels (131% of predicted). His blood pressure response to exercise was normal, and there was no significant upper-lower extremity blood pressure gradient at rest or post-exercise. His $\dot{V}_E/\dot{V}_{CO2}$ slope was elevated (Fig. 33.2, left middle panel) and his end-tidal pCO_2 was low, never exceeding 36 mm Hg throughout the study. His respiratory pattern was abnormal, characterized by rapid (respiratory rate = 83 breaths/min at peak exercise) and shallow (tidal volume at peak exercise only 25% of baseline vital capacity) breaths (Fig. 33.2, left lower panel). His baseline and post-exercise spirometric measurements, however, were completely normal.

No cardiologic or pulmonologic condition was identified that could plausibly explain the patient's unusual respiratory pattern during exercise. The most likely explanation for the respiratory findings was anxiety, which caused

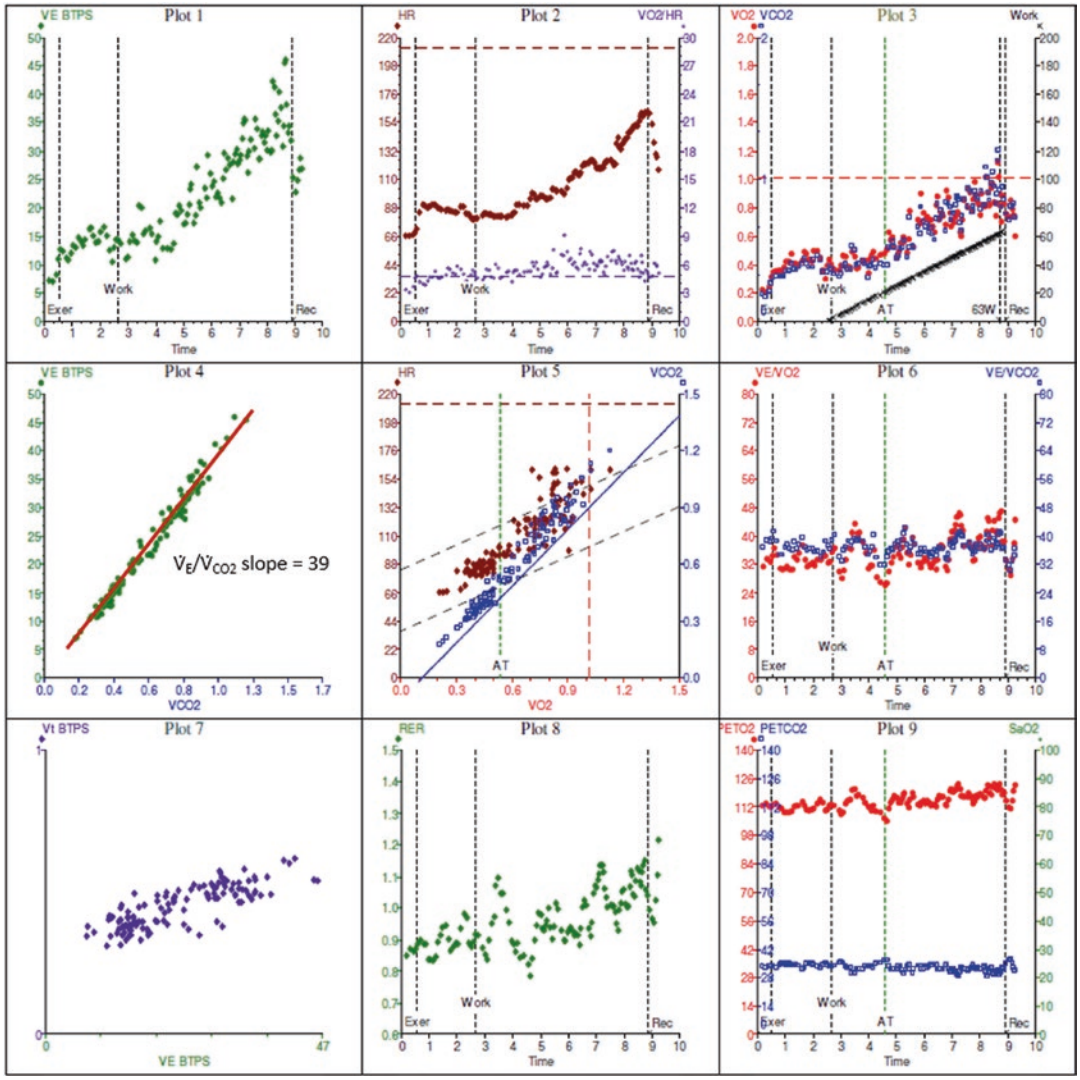


Fig. 33.2 Nine-panel graph of data from cardiopulmonary exercise test from patient 33.2: anxiety-related hyperventilation

him to hyperventilate (hence the low end-tidal pCO_2) and pant (hence the elevated respiratory rate and low tidal volume). When an individual pants, the dead space/tidal volume ratio is elevated, because tidal volume is low and physiologic dead space is unchanged. This causes gas exchange to be inefficient (i.e., one has to ventilate more in order to excrete a given quantity of CO_2) and explains why the $\dot{V}_E/\dot{V}_{CO2}$ slope is elevated. Anxiety-related hyperventilation is common among young children undergoing their first CPET study.

Of note, a similar pattern was also observed during Dr. Rhodes first CPET, which affirmed his wife's assertion that he often behaves like a child.

Case 33.3: Chronic Metabolic Alkalosis

The patient was a 19-year-old woman with a history of an eating disorder, characterized by binge eating and purging. She was referred for cardiologic evaluation on account of bradycardia at rest, and one episode of brief, self-resolving palpitations when her eating disorder was active. She was physically active, typically running 3–4 miles per day. She also participated in dance.

Her physical examination was normal except for a low heart rate. Her body mass index was 24.9 kg/m^2. Her electrocardiogram (EKG) revealed sinus bradycardia at a rate of 45 bpm but was otherwise within normal limits. An echocardiogram revealed normal cardiac structure and function. An exercise test was obtained to further assess her cardiopulmonary status and to evaluate for exercise-induced rhythm disturbances.

She performed a treadmill test using the Standard Bruce Protocol (Table 33.3 and Fig. 33.3). Her respiratory exchange ratio at peak exercise was 1.24, indicating that she expended a good effort. Her endurance time, peak $\dot{V}_{O2}$, and $\dot{V}_{O2}$ at the VAT were normal, as were her peak heart rate and oxygen pulse. Although her spirometric measurements were normal, her end-tidal pCO_2 was elevated to ~45–46 mm Hg throughout most of exercise (Fig. 33.3, right lower panel).

No cardiopulmonary condition was identified that could plausibly account for the mild end-tidal pCO_2 elevation. The most likely explanation for this phenomenon was a mild chronic metabolic alkalosis secondary to the patient's bulimia. This impression was supported by the observation that her serum HCO_3^- was mildly elevated (29 mM/L).

Table 33.3 Patient 33.3: chronic metabolic alkalosis. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	44.9
Peak $\dot{V}_{O2}$ (%predicted)	110
Endurance time	25th–50th percentile
Peak RER	1.24
Peak O_2 pulse (%predicted)	101
Peak heart rate (bpm)	181
Peak heart rate (%predicted)	90
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	49
End-tidal pCO_2 at VAT (mm Hg)	46
End-tidal pCO_2 during exercise	Slightly high
$\dot{V}_E/\dot{V}_{CO2}$ slope	21
Forced vital capacity (%predicted)	96
FEV1 (%predicted)	91
FEF 25–75 (%predicted)	85
Breathing reserve (%)	38
Rhythm	Sinus rhythm throughout study
Blood pressure response	Normal

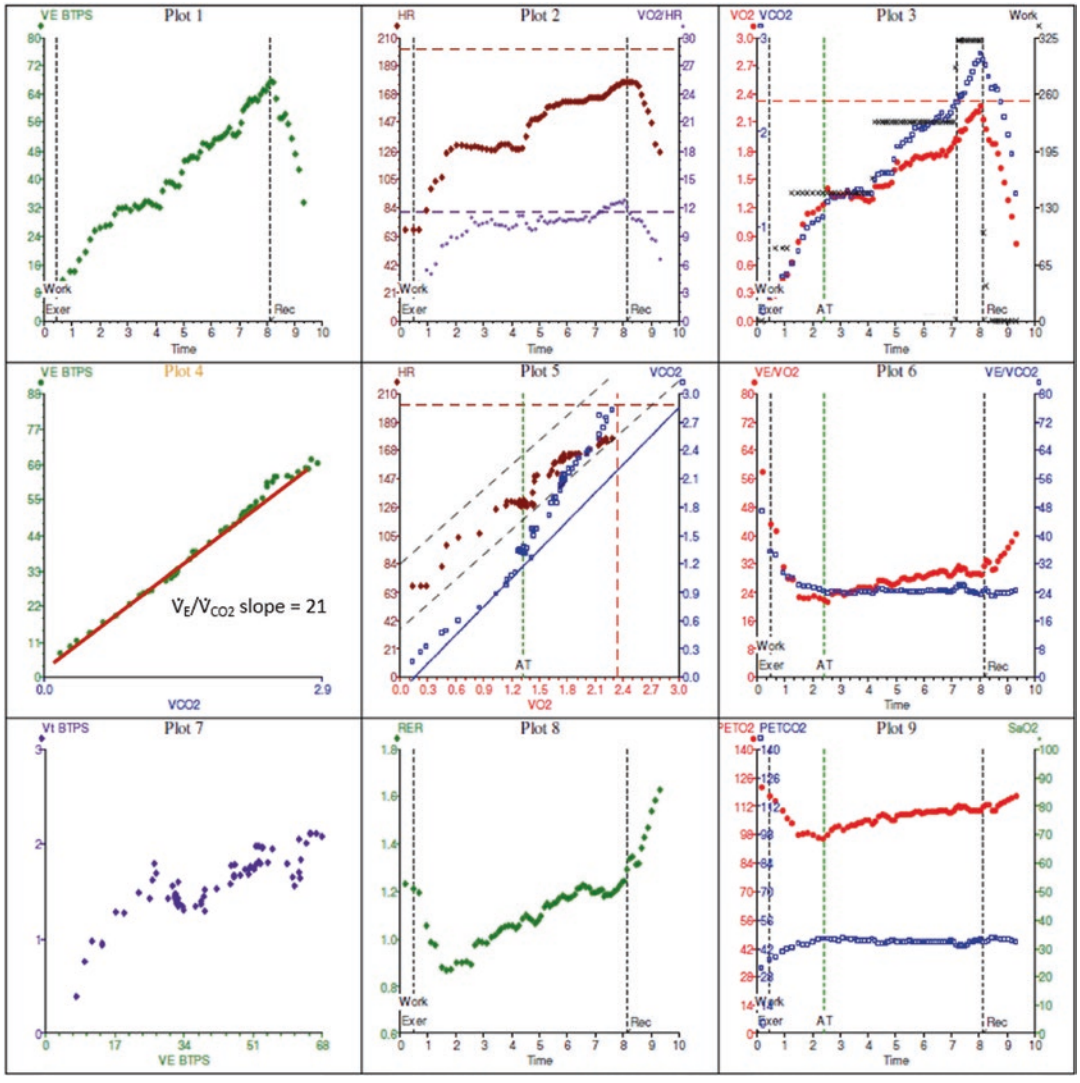


Fig. 33.3 Nine-panel graph of data from cardiopulmonary exercise test from patient 33.3: chronic metabolic alkalosis

Case 33.4: Anemia

The patient was a 15-year-old adolescent male with a history of sickle cell anemia (hemoglobin SS) who was referred for exercise testing on account of a history of chest pain. His past medical history was also significant for several (remote) episodes of acute chest syndrome as well as mild asthma.

His echocardiogram revealed no structural abnormalities. The left ventricle was mildly dilated but functioned well. There was no evidence of pulmonary hypertension. His hemoglobin at the time of the study was 8.8 gm/dl. A CPET was performed on a cycle ergometer with an 18 W/min ramp (Table 33.4 and Fig. 33.4).

The respiratory exchange ratio at peak exercise was 1.27, indicating that the patient expended a good effort. The peak work rate, peak $\dot{V}_{O2}$, and $\dot{V}_{O2}$ at the VAT were depressed. These abnormalities appeared to be due to an inability to increase the oxygen pulse appropriately. His heart rate increased more rapidly than normal during exercise, but his peak heart rate was normal (Fig. 33.4, middle panel). He did not experience chest pain during the study. No ST changes developed. His $\dot{V}_E/\dot{V}_{CO2}$ slope was slightly elevated and his end-tidal pCO_2 during exercise was slightly low. Exercise was terminated on account of general fatigue.

In this case, the low oxygen pulse at peak exercise was likely due to the low hemoglobin (rather than a low stroke volume), which reduced the blood's oxygen carrying capacity and, consequently, the delivery of oxygen to the tissues. This conjecture is based upon the fact that his hemoglobin was ~2/3 of the normal value for an adolescent male (comparable to the magnitude of the peak oxygen pulse depression), whereas his cardiac anatomy and function were documented to be normal. The excessive heart rate response to exercise reflected a compensatory response to the reduced oxygen delivery that resulted from the anemia. The mildly elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 may have been due to residual ventilation/perfusion mismatch resulting from the patient's past episodes of acute chest syndrome.

Table 33.4 Patient 33.4: anemia. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	26.0
Peak $\dot{V}_{O2}$ (%predicted)	59
Peak work rate (W)	80
Peak work rate (%predicted)	65
Peak RER	1.27
Peak O_2 pulse (%predicted)	65
Peak heart rate (bpm)	171
Peak heart rate (%predicted)	90
Heart rate increase	Excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	34
End-tidal pCO_2 at VAT (mm Hg)	36
End-tidal pCO_2 during exercise	Slightly low
$\dot{V}_E/\dot{V}_{CO2}$ slope	30
Forced vital capacity (%predicted)	65
FEV1 (%predicted)	68
FEF 25–75 (%predicted)	73
Breathing reserve (%)	54
Rhythm	Sinus rhythm throughout study
ST changes	None
Blood pressure response	Normal
Oxygen saturation at rest (%)	99
Oxygen saturation at peak exercise (%)	98

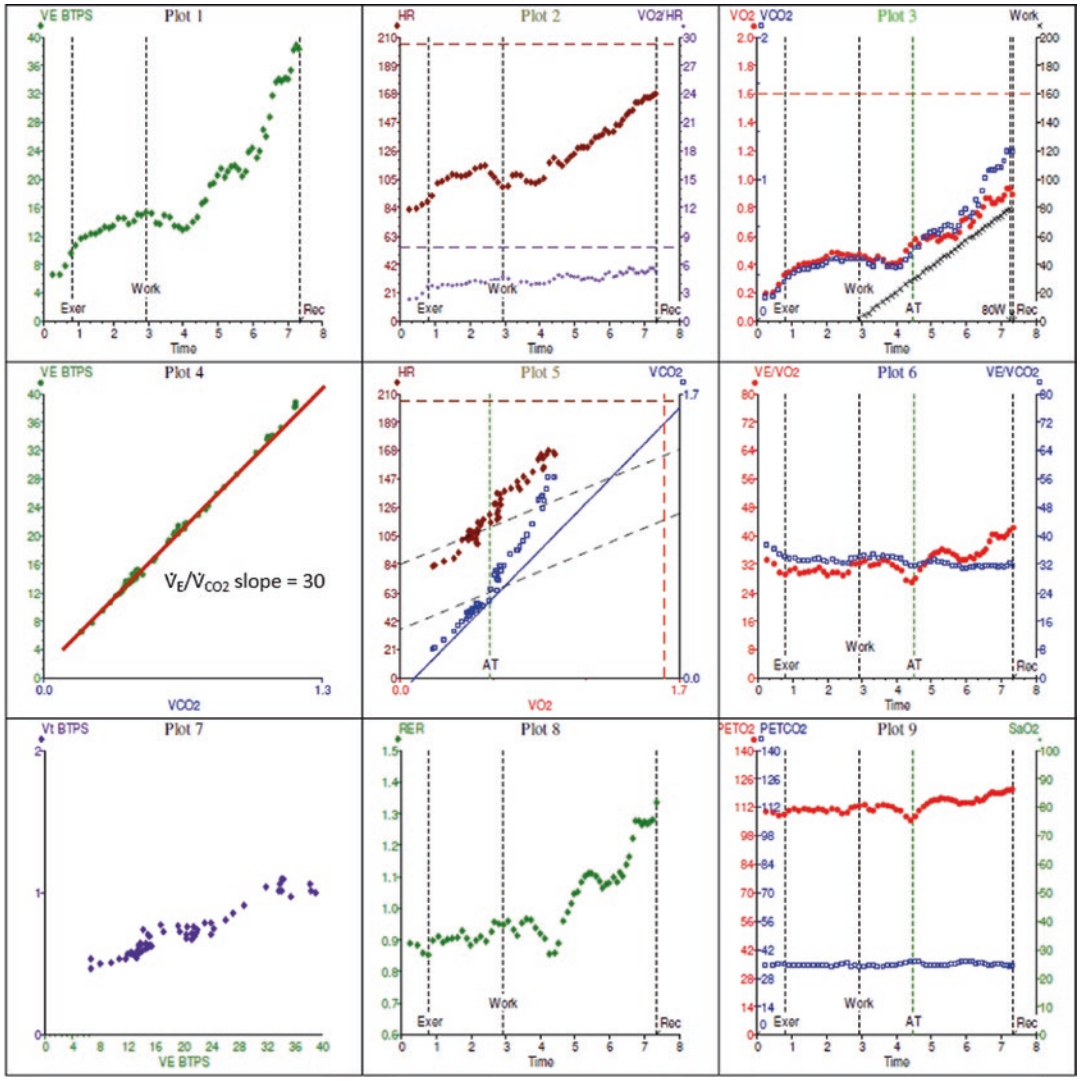


Fig. 33.4 Nine-panel graph of data from cardiopulmonary exercise test from patient 33.4: anemia

Case 33.5: Mitochondrial Myopathy s/p Heart Transplant

The patient was a 25-year-old woman s/p heart transplant 9 years earlier for a dilated cardiomyopathy associated with a mitochondrial disorder affecting the function of cytochrome c in the electron transport chain. She had done well from a cardiologic perspective following her transplant, without episodes of significant rejection. At the time of the exercise test, she denied recent cardiopulmonary symptoms. Although she was not engaging in formal exercise, she did do yoga at least once a week. She also worked full time as a fifth grade teacher, walked over a mile to and from work, and would regularly participate with her students during gym class and recess.

A recent cardiac catheterization detected no evidence of coronary artery disease. Her cardiac index was normal (3.7 l/min/m^2), but her mean pulmonary artery pressure and mean pulmonary capillary wedge pressure were mildly elevated (20 and 14 mm Hg, respectively). An endomyocardial biopsy detected no evidence of rejection. A CPET with stress echocardiography was obtained (Table 33.5 and Fig. 33.5) to further characterize

Table 33.5 Patient 33.5: mitochondrial myopathy s/p heart transplant. Selected data from the cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	19.7
Peak $\dot{V}_{O2}$ (%predicted)	52
Endurance time (percentile)	<10th
Peak RER	1.20
Peak O_2 pulse (%predicted)	57
Peak heart rate (bpm)	181
Peak heart rate (%predicted)	93
Heart rate increase	Excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	37
End-tidal pCO_2 at VAT (mm Hg)	36
End-tidal pCO_2 during exercise	Slightly low
$\dot{V}_E/\dot{V}_{CO2}$ slope	34
Forced vital capacity (%predicted)	98
FEV1 (%predicted)	110
FEF 25–75 (%predicted)	118
Peak tidal volume (%FVC)	41
Peak respiratory rate (breaths/min)	31
Breathing reserve (%)	67
Rhythm	Sinus rhythm throughout study
ST changes	Non-specific
Blood pressure response	Normal
Oxygen saturation at rest (%)	99
Oxygen saturation at peak exercise (%)	99

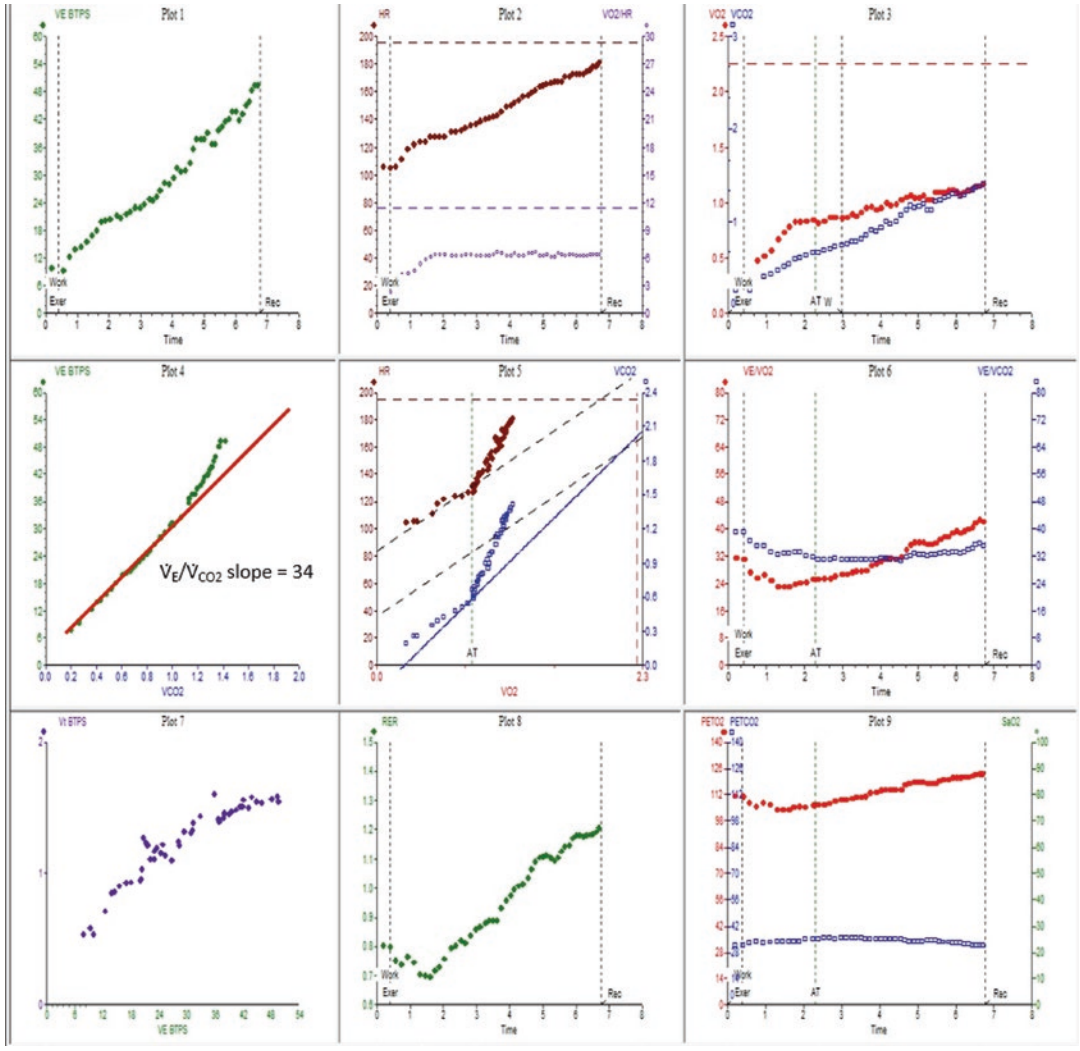


Fig. 33.5 Nine-panel graph of data from cardiopulmonary exercise test from patient 33.5: mitochondrial myopathy s/p heart transplant

her current cardiopulmonary status. The Bruce treadmill protocol was used for the study.

The respiratory exchange ratio at peak exercise was 1.20, indicating that a good effort was expended. Her endurance time, peak $\dot{V}_{O2}$, and $\dot{V}_{O2}$ at the VAT were low. The oxygen pulse at peak exercise was also quite low. Her peak heart rate was normal, and her heart rate increased excessively for her level of oxygen consumption during exercise (Fig. 33.5, middle panel). Her $\dot{V}_E/\dot{V}_{CO2}$ slope was elevated and her end-tidal pCO_2 during exercise was slightly low. She nevertheless had a large breathing reserve at peak exercise, and her tidal volume and respiratory rate at peak exercise were slightly low. Stress echocardiography revealed normal baseline valvular and ventricular systolic function. The right ventricular pressure, based upon a small tricuspid insufficiency jet, was estimated to be 26 mm Hg plus the right atrial v-wave. The ventricular function enhanced appropriately post-exercise and became hyperdynamic. There were no wall motion abnormalities. The tricuspid insufficiency jet estimated a right ventricular pressure or 35 mm Hg plus the right atrial v-wave. No left ventricular outflow tract obstruction was detected.

In light of the normal ventricular systolic function documented by the stress echocardiography, it is likely that the low endurance time, peak $\dot{V}_{O2}$, and peak oxygen pulse were primarily due to decreased peripheral oxygen extraction secondary to the mitochondrial myopathy, rather than an impairment of the stroke volume response to exercise. (Although neither invasive blood sampling nor near infrared spectroscopy was employed in this study, based upon the echocardiographic and CPET data, one would expect that the normal exercise-related decline in mixed oxygen saturation would not have been observed.) The low VAT reflected the skeletal muscles' (but not the transplanted heart's!) early and excessive reliance upon anaerobic metabolism, because of the impaired synthesis of ATP via aerobic metabolism. The excessive heart rate response to exercise probably reflected her body's attempt to compensate for her inability to extract oxygen from the blood. The elevated breathing reserve and relatively low peak-exercise tidal volume and respiratory rate probably reflected the fact that the patient was unable to increase her metabolic rate to normal levels at peak exercise, because her mitochondrial defect prevented her muscles from generating the ATP required to support more intense physical activity. Mild diastolic dysfunction, common in patients 9 years after cardiac transplant, was also probably present and was reflected by the mildly elevated pulmonary capillary wedge pressure. Ventilation/perfusion mismatch secondary to this phenomenon also probably accounted for the elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2.

It is interesting to note that the patient was asymptomatic, despite the profound abnormalities detected on formal CPET. This probably reflected the fact that, although the heart transplant had restored her cardiac function, the patient's skeletal muscles continued to be, and had always been, afflicted by the mitochondrial myopathy, both before and after the transplant. She therefore never knew what it was like to have normal exercise function.

Case 33.6: Complete Heart Block

The patient was a 25-year-old woman with congenital complete heart block with a narrow complex junctional escape rhythm. She was well adapted and had played collegiate hockey. She continued to be physically active after graduation from college and was managed with yearly surveillance that included Holter monitoring, echocardiography, and periodic exercise tests. At the time of the exercise test, she was asymptomatic. However, her Holter monitor revealed that her escape rhythm had had at times declined to as low as 30 bpm. Her echocardiogram revealed stable, mild left ventricular dilation (end diastolic volume Z-score 2.4) with normal, stable function (ejection fraction 0.63).

A cardiopulmonary exercise test was performed (Table 33.6) using the Bruce treadmill protocol. She achieved a peak respiratory

Table 33.6 Patient 33.6: complete heart block. Selected data from the pre and post-pacemaker cardiopulmonary exercise tests

Parameter	Pre-pacemaker	Post-pacemaker
Peak $\dot{V}_{O2}$ (ml/kg/min)	42.8	46.7
Peak $\dot{V}_{O2}$ (%predicted)	119	122
Endurance time (min)	21:00	21:00
Endurance time (%ile)	>90th	>90th
Peak RER	1.25	1.11
Peak O_2 pulse (%predicted)	162	131
Peak heart rate (bpm)	144	181
Peak heart rate (%predicted)	74	93
Heart rate increase	Depressed	Normal
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	71	72
End-tidal pCO_2 at VAT (mm Hg)	42	40
End-tidal pCO_2 during exercise	Normal	Normal
$\dot{V}_E/\dot{V}_{CO2}$ slope	26	28
Breathing reserve (%)	40	43
Rhythm	CHB with junctional escape	A-sensed/V-paced
Blood pressure response	Normal	Normal

exchange ratio of 1.25 and was able to complete the protocol. Her peak $\dot{V}_{O2}$ was excellent (119%predicted). Her cardiac rhythm was complete heart block with a narrow complex, junctional escape rhythm throughout the study. Her peak heart rate was depressed (74%predicted). Her oxygen pulse at peak exercise was supranormal (162%predicted), indicating that her heart's ability to compensate for the chronotropic defect was excellent. Her gas exchange during exercise was normal. Stress echocardiography revealed normal augmentation of cardiac function.

On account of the Holter monitor results and concern for long-term prevention of Stokes-Adams attacks, mitral valve deterioration, and cardiac arrest, she had implantation of a transvenous dual-chamber pacemaker. On a follow-up treadmill exercise test following pacemaker implantation (Table 33.6), she once again completed the Bruce protocol. Her respiratory exchange ratio at peak exercise was 1.11, suggesting that she expended an adequate effort, but perhaps not quite as good as on her pre-pacemaker study. Her peak $\dot{V}_{O2}$ was slightly higher than on her previous study. Her pacemaker functioned appropriately. Her rhythm was A-sensed/V-paced throughout the study, and her peak heart rate was 181 bpm (93%predicted). Her oxygen pulse at peak exercise was correspondingly lower than it had been on her pre-pacemaker study.

This case demonstrates that patients can sometimes compensate for significant chronotropic impairment by increasing their stroke volume (as reflected by the supranormal oxygen pulse). It is likely that the patient's athletic lifestyle contributed to this phenomenon. Implantation of a pacemaker allowed the patient to have a more normal heart rate response to exercise and restored atrial-ventricular synchrony. However, because the ventricles had less time to fill at the higher heart rate, the stroke volume at peak exercise was lower than it had been for pre-pacemaker implantation, and the patient's peak $\dot{V}_{O2}$ was minimally increased. It should also be acknowledged that the peak-exercise respiratory exchange ratio was higher on the pre-pacemaker study. This fact suggests that exercise termination on that study may have been closer to the patient's true maximal capacity and that the beneficial hemodynamic effects of the pacemaker implantation may not have been fully exposed in the post-pacemaker study.

Case 33.7: Obesity

The patient was a 16-year-old woman with a history of asthma and obesity. She presented on account of a recent history of chest pain and worsening dyspnea on exertion. A cardiopulmonary exercise test (Table 33.7 and Fig. 33.6) was undertaken to further assess her symptoms. Exercise was performed on a cycle ergometer with a 20 W/min ramp. At the time of the test, the patient weighed 120 kg with a body mass index of 44.1 kg/m^2.

The respiratory exchange ratio at peak exercise was 1.24, indicating that an adequate effort

Table 33.7 Patient 33.7: obesity. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	15.0
Peak $\dot{V}_{O2}$ (%predicted)	96
Peak work rate (W)	129
Peak work rate (%predicted)	77
Peak RER	1.24
Peak O_2 pulse (%predicted)	99
Peak heart rate (bpm)	184
Peak heart rate (%predicted)	97
Heart rate increase	Normal
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	71
End-tidal pCO_2 at VAT (mm Hg)	43
End-tidal pCO_2 during exercise	Slightly elevated at peak
$\dot{V}_E/\dot{V}_{CO2}$ slope	23
Baseline spirometry	Mild obstructive pattern
Post-exercise spirometry	Normal
Tidal volume at peak exercise (%FVC)	38
Respiratory rate at peak exercise (breaths/min)	39
Breathing reserve (%)	52
Rhythm	Sinus
ST changes	None
Blood pressure response	Appropriate
Oxygen saturation at rest (%)	98
Oxygen saturation at peak exercise (%)	98

was expended. Although her weight-normalized peak $\dot{V}_{O2}$ was low, her %predicted peak $\dot{V}_{O2}$ was normal. Her peak work rate was only mildly depressed, and the $\dot{V}_{O2}$ at the VAT was normal. Her oxygen pulse at peak exercise was normal, and although she had mild sinus tachycardia at rest, her heart rate increased appropriately during exercise. Her $\dot{V}_E/\dot{V}_{CO2}$ slope was normal, but her end-tidal pCO_2 at peak exercise was elevated. She had a normal breathing reserve at peak exercise. The expected decline in end-tidal pCO_2 at higher levels of exercise was not observed. Her tidal volume at peak exercise was slightly low. Her baseline spirometry revealed a mild obstructive pattern, which improved and normalized post-exercise. Her blood pressure increased appropriately during exercise. She developed her typical symptoms during exercise. There were no EKG or hemodynamic correlates.

The disproportionately low weight-normalized peak $\dot{V}_{O2}$ reflects the fact that obesity is associated with a large amount of adipose tissue, which does not consume much oxygen during exercise. Under these circumstances, merely normalizing $\dot{V}_{O2}$ for weight may be misleading, as the resulting value does not accurately reflect the cardiopulmonary system's ability to provide oxygen to the skeletal muscles during exercise or the skeletal muscles' capacity to consume oxygen. The discrepancy between her %predicted peak work rate and %predicted peak $\dot{V}_{O2}$ probably reflects the fact that she must expend an abnormally large amount of energy moving her heavy legs and chest wall during exercise and therefore can devote less energy to the work of moving the pedals. This discrepancy would likely be magnified if she were to have performed treadmill exercise and had to bear her entire weight throughout the study (on the cycle ergometer, most of her weight is borne by the bicycle seat). Similarly, the CO_2 retention at higher levels of exercise probably reflects the fact that moving her heavy chest wall at higher levels of exercise is difficult. It is therefore energetically more favorable to employ a breathing strategy characterized by a low tidal volume, less ventilation, and mild CO_2 retention. These findings and adaptations are typical of patients with obesity.

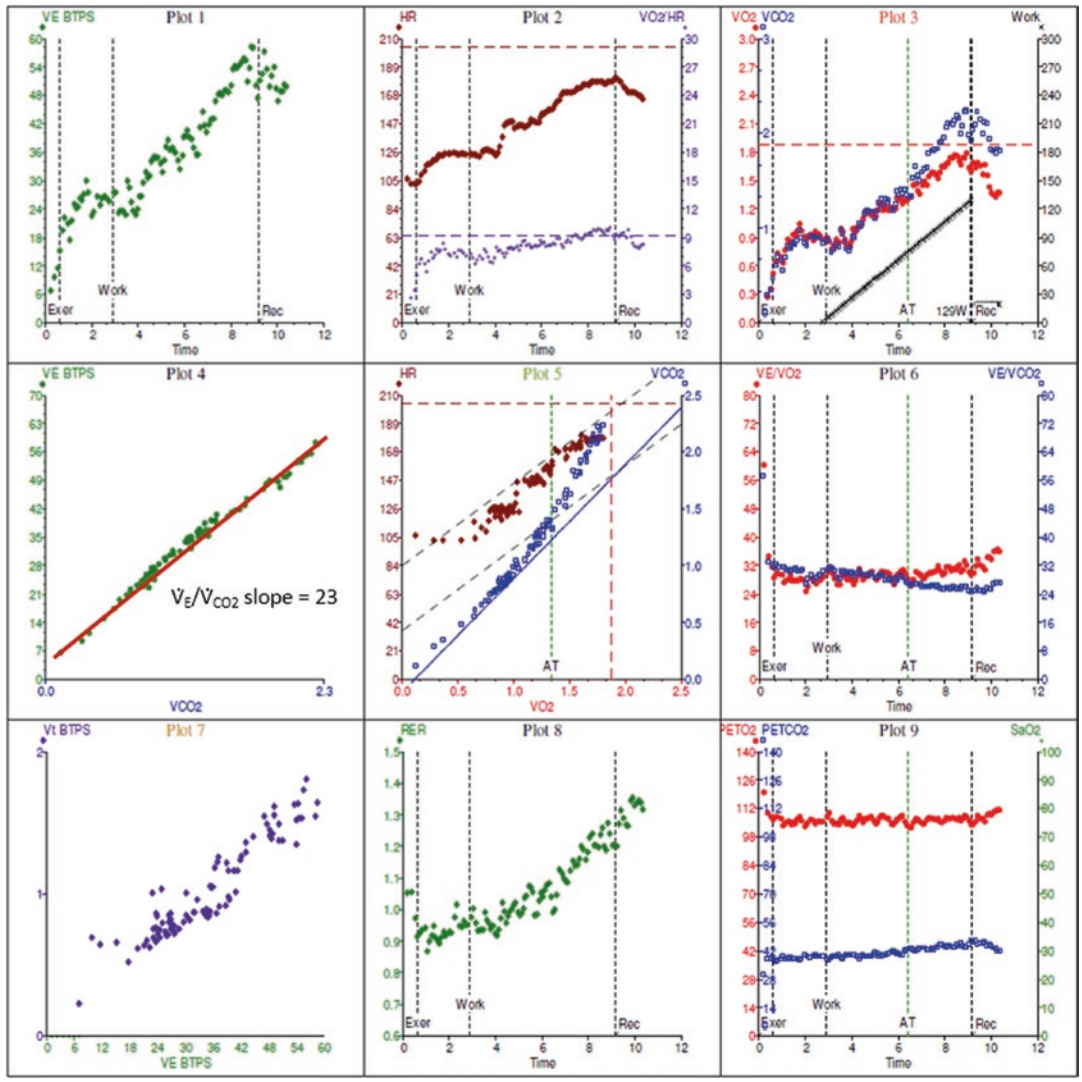


Fig. 33.6 Nine-panel graph of data from cardiopulmonary exercise test from patient 33.7: obesity

Case 33.8: An Athlete with Shortness of Breath

The patient was a 22-year-old college senior who was referred for evaluation of dyspnea on exertion and resting bradycardia. He was a competitive long-distance runner (usually 3 K and 5 K races) but complained that over the past year, he had been developing shortness of breath during his runs. He was able to finish the races but tended to be short of breath throughout and was sometimes dizzy upon completing the race. He denied any symptoms of chest pain and palpitations and had never experienced syncope. His EKG revealed sinus arrhythmia/sinus bradycardia but was otherwise within normal limits. His echocardiogram revealed mild left ventricular dilation and mild eccentric ventricular hypertrophy (increased left ventricular mass with normal mass/volume ratio) with normal ventricular function. A Holter monitor documented

sinus bradycardia to as low as 31 bpm during sleep; no significant ectopy was detected. A cardiopulmonary exercise test was obtained (Table 33.8 and Fig. 33.7) to further assess his symptoms.

The patient exercised on a treadmill using the standard Bruce protocol. The first two stages were electively abbreviated on account of his high level of fitness. He completed the protocol and ran for an additional 31 s at a speed of 6.5 mph and a grade of 22%. He developed his typical symptoms of shortness of breath in mid exercise. These symptoms worsened as the test progressed. Exercise was terminated on account of shortness of breath and leg fatigue. His respiratory exchange ratio at peak exercise was 1.10, indicating that he expended an adequate effort. His peak $\dot{V}_{O2}$, peak oxygen pulse, and $\dot{V}_{O2}$ at the VAT were excellent. His peak heart rate was in the normal range, but his heart rate during exercise was low relative to his $\dot{V}_{O2}$ (Fig. 33.7, middle panel). His tidal volume increased appropriately during exercise and his gas exchange during exercise was normal. His breathing reserve at peak exercise was low, however. Baseline spirometry reproducibly revealed a mild obstructive pattern. Post-exercise spirometry was considerably improved, with normalization of all parameters.

Despite the patient's presenting symptoms, the CPET documented that the he was capable of exercising to extremely high levels of aerobic function. (Based upon his peak RER and peak heart rate, it is likely that he could have gone even further!) He was able to achieve the high levels of exercise by increasing his oxygen pulse to levels far beyond expected values. This phenomenon is commonly encountered in endurance athletes and is due primarily to an above average stroke volume during exercise. The increased left ventricular volume on his resting echocardiogram also reflects this physiology. (His resting bradycardia is another manifestation of this phenomenon. His stroke volume is higher than normal, even at rest, and he can therefore maintain a normal cardiac output at a lower heart rate.) Increased oxygen extraction at peak exercise (compared to normal individuals) is also encountered in endurance athletes and probably also contributed to the patient's high oxygen pulse at peak exercise.

Table 33.8 Patient 33.8: An athlete with shortness of breath. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	71.3
Peak $\dot{V}_{O2}$ (%predicted)	140
Endurance time (%ile)	>90th
Peak RER	1.10
Peak O_2 pulse (%predicted)	148
Peak heart rate (bpm)	187
Peak heart rate (%predicted)	94
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	84
End-tidal pCO_2 at VAT (mm Hg)	40
End-tidal pCO_2 during exercise	Normal
Breathing reserve (%)	7
$\dot{V}_E/\dot{V}_{CO2}$ slope	25
Baseline forced vital capacity (%predicted)	87
Baseline FEV1 (%predicted)	80
Baseline FEV1/FVC (%)	78
Baseline FEF 25–75 (%predicted)	63
Post-exercise forced vital capacity (%predicted)	97
Post-exercise FEV1 (%predicted)	97
Post-exercise FEV1/FVC (%)	84
Post-exercise FEF 25–75 (%predicted)	105
Baseline arterial O_2 saturation (%)	99
Peak-exercise arterial O_2 saturation (%)	98
Rhythm	Rare PVC near peak exercise
ST abnormalities	None
Blood pressure response	Normal

The abnormal baseline spirometry was consistent with a degree of bronchoconstriction. On the day of the CPET, exercise appeared to relieve the baseline bronchoconstriction (as is commonly the case). Under other circumstances and in different environments (e.g., in cold air or in the presence of high pollen concentrations or other pulmonary irritants), it is possible that the bronchoconstriction would not be relieved or, indeed, might worsen with exercise. This physiology

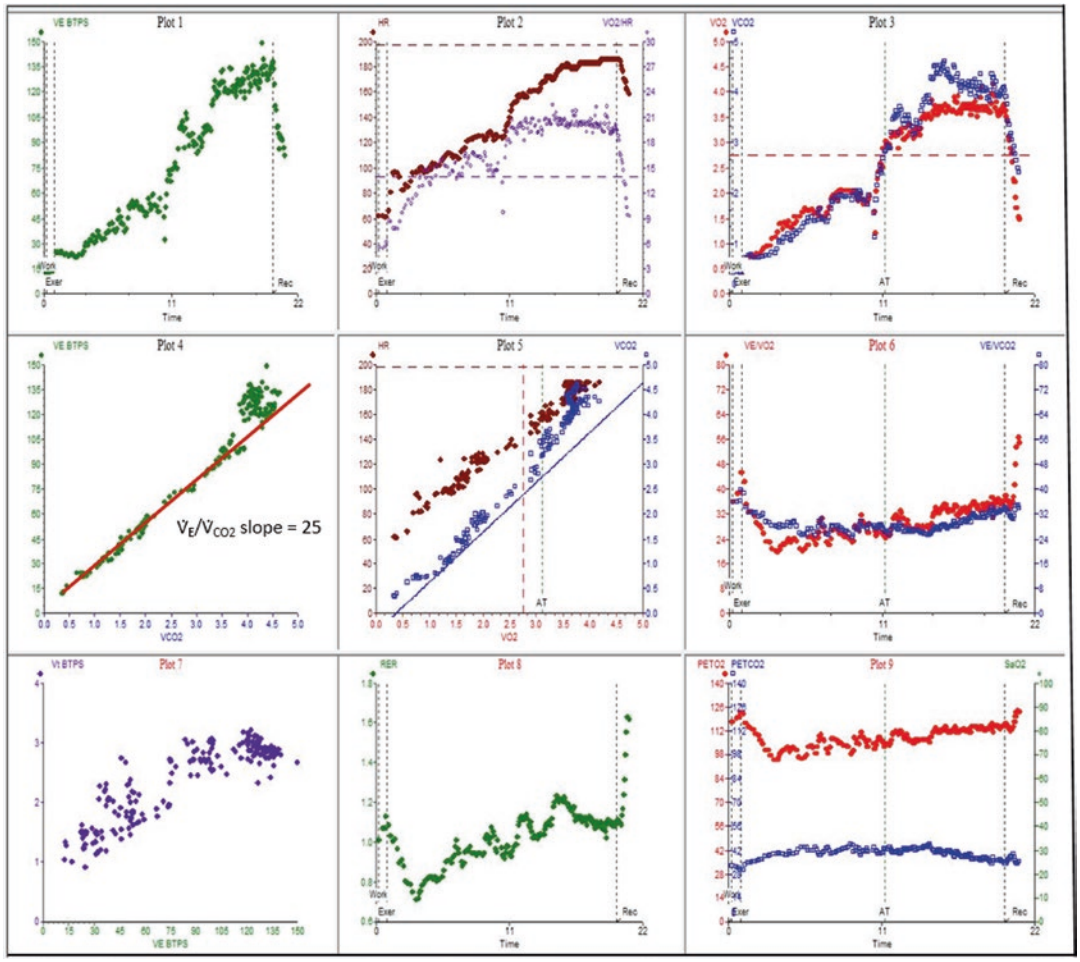


Fig. 33.7 Nine-panel graph of data from cardiopulmonary exercise test from patient 33.8: athlete with shortness of breath

could certainly account for his symptoms of dyspnea.

The low breathing reserve at peak exercise is (paradoxically) commonly encountered in endurance athletes, even in the absence of lung disease. It arises because their cardiovascular function is supranormal and they can increase their metabolic rate (and CO_2 production) to very high levels. They therefore must ventilate more at peak exercise and use a greater fraction of their breathing reserve. In this patient, the breathing reserve was low (~20%) even when the post-exercise volume exhaled in the first second of forced expiration (FEV1) was used to calculate the maximum voluntary ventilation and breathing reserve (see Chap. 11).

Case 33.9: Athlete with Post-viral Chronic Fatigue Syndrome

The patient was a 17-year-old adolescent female who was diagnosed with chronic fatigue syndrome and orthostatic dizziness following a viral illness approximately 1 year prior to this evaluation. She responded well to psychotherapy and low-dose antidepressant medications. She had become captain of her high school's basketball team and her symptoms had virtually resolved. A cardiopulmonary exercise test was obtained to further assess her current status. A cycle ergometer with a 25 W/min ramp was employed for the study (Table 33.9 and Fig. 33.8).

The patient's respiratory exchange ratio at peak exercise was 1.11, indicating that an adequate effort was expended. Her %predicted peak work rate, peak $\dot{V}_{O2}$, and peak oxygen pulse were exceptionally high. The $\dot{V}_{O2}$ at the ventilatory anaerobic threshold was also high. Her peak heart rate was normal, but her heart rate tended to be low for her level of $\dot{V}_{O2}$ during exercise (Fig. 33.8, middle panel). Her end-tidal pCO_2 was mildly elevated at higher levels of exercise but declined appropriately near peak exercise (Fig. 33.8, right lower panel).

The patient's excellent aerobic function was characteristic of endurance athletes (e.g., basketball team captains). She was able to achieve the high levels of exercise by increasing her oxygen pulse to levels far beyond expected values. The robust oxygen pulse at peak exercise was probably due primarily to a large stroke volume at peak exercise (also characteristic of endurance athletes). Increased oxygen extraction at peak exercise may also have contributed to the large oxygen pulse. Because of her large stroke volume, she was able to increase her cardiac output during exercise without raising her heart rate as much as a normal, nonathlete would, and her heart rate for any given level of $\dot{V}_{O2}$ therefore tended to be low.

The elevated end-tidal pCO_2 at higher levels of exercise was probably due to the large quantity of CO_2 that was being delivered to the alveoli, which resulted in a gradient between the end-tidal pCO_2 and the arterial pCO_2 (see Chap. 12).

Table 33.9 Patient 33.9: athlete with post-viral chronic fatigue syndrome. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	44.7
Peak $\dot{V}_{O2}$ (%predicted)	151
Peak work rate (W)	267
Peak work rate (%predicted)	178
Peak RER	1.11
Peak O_2 pulse (%predicted)	156
Peak heart rate (bpm)	182
Peak heart rate (%predicted)	97
Blood pressure response	Normal
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	88
End-tidal pCO_2 at VAT (mm Hg)	46
End-tidal pCO_2 during exercise	Normal
Peak respiratory rate (breaths/min)	46
Peak tidal volume (%FVC)	49
Breathing reserve (%)	39
$\dot{V}_E/\dot{V}_{CO2}$ slope	21
Baseline forced vital capacity (%predicted)	92
Baseline FEV1 (%predicted)	99
Baseline FEV1/FVC (%)	92
Baseline FEF 25–75 (%predicted)	113
Rhythm	Sinus throughout
ST abnormalities	None

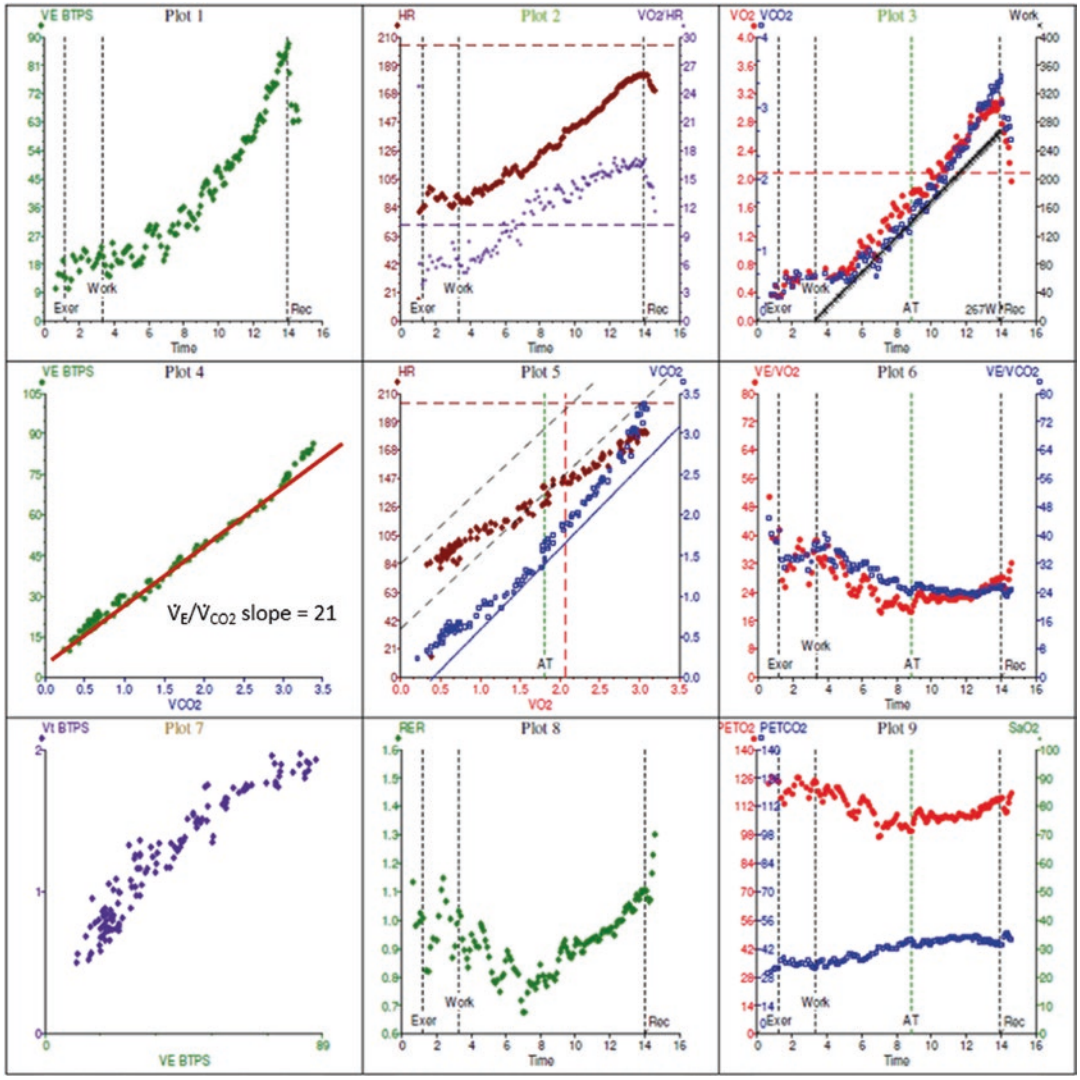


Fig. 33.8 Nine-panel graph of data from cardiopulmonary exercise test from patient 33.9: athlete with post-viral chronic fatigue syndrome

The decline in end-tidal pCO_2 near peak exercise (i.e., above the respiratory compensation point) probably reflected the fact that the patient generated a respiratory alkalosis in response to the lactic (metabolic) acidosis that accumulated at high exercise intensity. This decline would be uncharacteristic of patients who develop CO_2 retention due to respiratory disease. The patient's normal baseline spirometry, breathing reserve, peak respiratory rate, and tidal volume at peak exercise also suggest that the elevated end-tidal pCO_2 levels were not related to respiratory disease.

Reference

1. Gratz A, Hess J, Hager A. Self-estimated physical functioning poorly predicts actual exercise capacity in adolescents and adults with congenital heart disease. Eur Heart J. 2009;30(4):497–504.

34 Patients with Unusual Congenital Heart Defects and/or Intracardiac Shunts

Jonathan Rhodes

Case 34.1: Fontan Patient with Sinus Node Dysfunction

The patient was a 12-year-old girl who was born with tricuspid atresia/pulmonary atresia. She underwent surgical implantation of a 3.5 mm modified Blalock–Taussig shunt when she was 2 days old followed by a bidirectional Glenn shunt when she was 7 months old and lateral tunnel fenestrated Fontan procedure when she was 20 months old. Following this surgery, she also required transcatheter left pulmonary artery dilation/stenting for pulmonary artery stenosis. Her fenestration was electively occluded at that time. On a cardiac catheterization performed 1 year prior to the exercise test, she had excellent hemodynamics, with Fontan pathway pressure of 14 mm Hg and ventricular end diastolic pressure of 6–7 mm Hg. No significant residual pulmonary artery stenoses were present. Some venovenous collaterals (from innominate vein to left upper pulmonary vein) were occluded at that time. She did well thereafter, with normal exercise capacity and no cardiopulmonary symptoms. She was maintained only on aspirin and an angiotensin-converting enzyme inhibitor. She was referred to the exercise laboratory to further assess her current cardiopulmonary status.

The exercise test was performed on a cycle ergometer with an 18 W/min ramp (Table 34.1 and Fig. 34.1). She achieved a peak respiratory exchange ratio of 1.10, indicating that an adequate effort was expended. Her peak work rate was normal and her peak $\dot{V}_{O2}$ was only mildly depressed. Her peak heart rate was only 73%predicted, and

Table 34.1 Patient 34.1: Fontan patient with sinus node dysfunction. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	22.0
Peak $\dot{V}_{O2}$ (%predicted)	81
Peak work rate (W)	191
Peak work rate (%predicted)	111
Peak RER	1.10
Peak O_2 pulse (%predicted)	110
Peak heart rate (bpm)	141
Peak heart rate (%predicted)	73
Heart rate increase	Depressed
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	47
End-tidal pCO_2 at VAT (mm Hg)	36
End-tidal pCO_2 during exercise	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	34
Rhythm	See text
Blood pressure response	Normal
Oxygen saturation at rest (%)	90
Oxygen saturation at peak exercise (%)	87

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_34

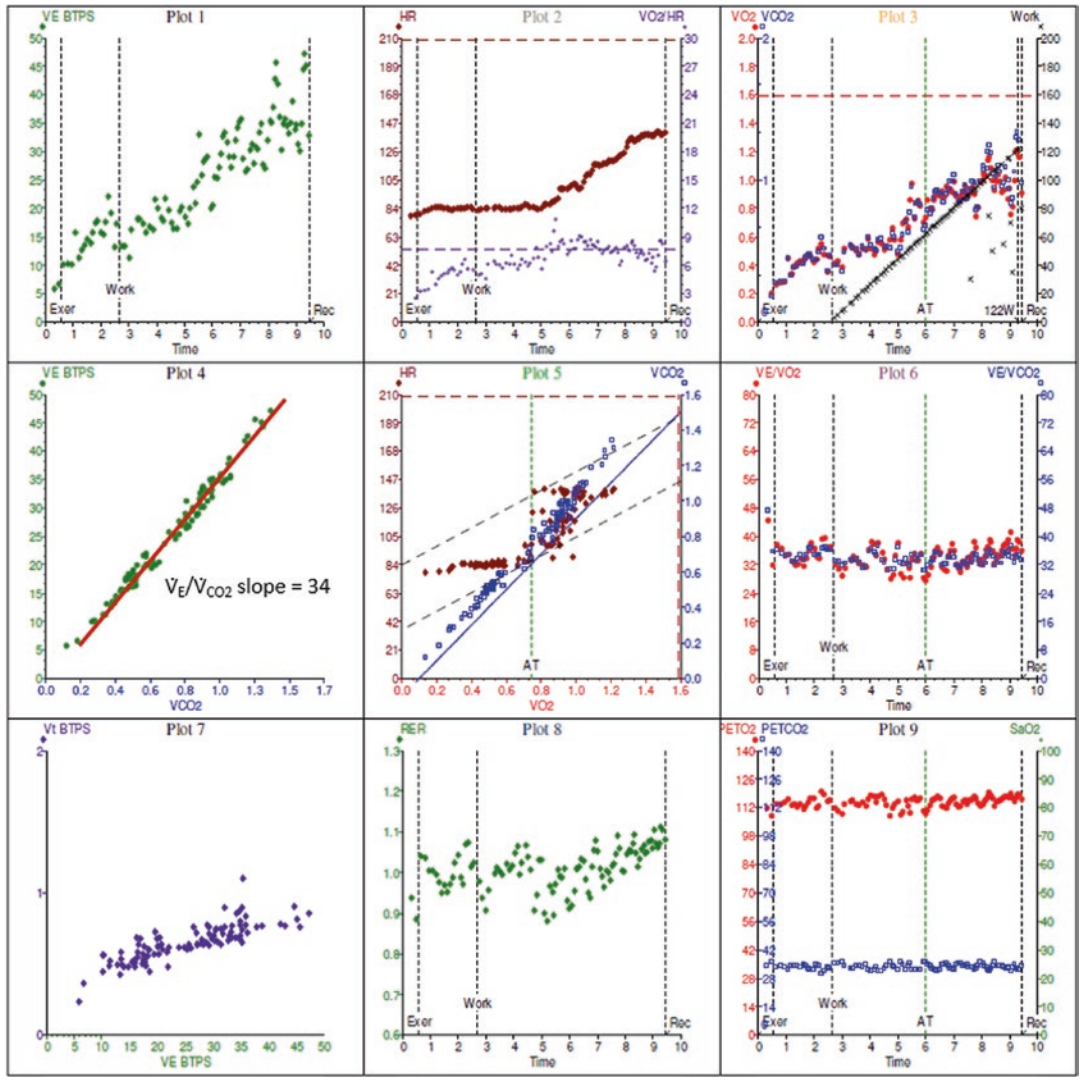


Fig. 34.1 Nine-panel graph of data from cardiopulmonary exercise test from patient 34.1: Fontan patient with sinus node dysfunction. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise, PETCO2 end-tidal pCO2, PETO2 end-tidal pO2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, $\dot{V}_{O2}$ oxygen consumption, $\dot{V}_{O2}$/HR oxygen pulse

her heart rate increase during exercise was blunted (middle panel and upper middle panel of Fig. 34.1). Her oxygen pulse at peak exercise was excellent (110%predicted). Mild arterial desaturation was present at rest and worsened slightly at peak exercise. Her baseline rhythm was ectopic atrial at ~75 bpm. Sinus rhythm emerged by mid-exercise. The ectopic atrial rhythm returned by ~2 min of recovery. No other ectopy was detected. The $\dot{V}_E/\dot{V}_{CO2}$ slope was elevated, and end-tidal pCO_2 during exercise was low (left middle panel and right lower panel of Fig. 34.1). The exercise test was terminated due to shortness of breath.

The low peak heart rate and the atrial escape rhythm present at rest are consistent with a degree of sinus node dysfunction—a condition commonly encountered among Fontan patients. The patient was able to compensate for the low peak heart rate by increasing her stroke volume to above-average levels. Consequently, her peak

work rate was normal and her peak $\dot{V}_{O2}$ only mildly depressed. This accommodation was probably the result of the Starling mechanism; i.e., the ventricle had more time to fill at the lower heart rate and therefore was able to eject a larger volume of blood with each beat. The low arterial saturation at rest was probably the result of physiologic right-to-left shunting across residual veno-venous collaterals (also common in Fontan patients). The decline in arterial oxygen saturation with exercise was probably the result of increased extraction of oxygen from the blood during exercise. The blood that was shunted right to left via the venovenous collaterals therefore had a lower oxygen saturation and lowered the arterial oxygen saturation further (compared to at rest) when it mixed with the blood returning from the lungs. It is also possible that the magnitude of the right-to-left shunting across the veno-venous collaterals increased as the Fontan pressures increased (and the left atrial pressures probably decreased) during exercise. The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 were probably the result of the right-to-left shunting and/or the pulmonary blood flow maldistribution and consequent ventilation/perfusion mismatch commonly encountered in Fontan patients (see Chap. 15). The patient's disproportionately low weight-normalized $\dot{V}_{O2}$ was due to mild obesity (body mass index [BMI] 94th percentile).

Case 34.2: Hypoplastic Left Heart Syndrome, s/p Fontan, and Second-Degree Heart Block

The patient was a 12-year-old boy who was born with hypoplastic left heart syndrome. He had undergone a Stage 1 procedure when he was a neonate, followed by a bidirectional Glenn procedure when he was 8 months old and a fenestrated Fontan procedure when he was 4 years old. His fenestration was electively closed in the catheterization laboratory when he was 7 years old. He did well following these procedures. At the time of his evaluation, he denied any cardiopulmonary symptoms and claimed to be active without exercise intolerance. His echocardiogram revealed good right ventricular function and only mild tricuspid regurgitation. His Fontan pathway appeared unobstructed. No residual shunt was identified. A cardiopulmonary exercise test was obtained to further assess his current status (Table 34.2 and Fig. 34.2).

Table 34.2 Patient 34.2: hypoplastic left heart syndrome, s/p Fontan, and second-degree heart block. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	26.7
Peak $\dot{V}_{O2}$ (%predicted)	57
Peak work rate (W)	64
Peak work rate (%predicted)	59
Peak RER	1.19
Peak O_2 pulse (%predicted)	134
Peak heart rate (bpm)	81
Peak heart rate (%predicted)	42
Heart rate increase	Depressed
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}o_2$)	28
End-tidal pCO_2 at VAT (mm Hg)	35
End-tidal pCO_2 during exercise	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	45
Rhythm	Sinus→2:1 block
Blood pressure response	Normal
Oxygen saturation at rest (%)	97
Oxygen saturation at peak exercise (%)	97

The CPET was performed on a cycle ergometer with a 10 W/min ramp. His respiratory exchange ratio at peak exercise was 1.11, indicating that an adequate effort was expended. His peak $\dot{V}_{O2}$ and peak work rate were significantly depressed. Although he was in sinus rhythm with first-degree atrioventricular (AV) block at rest, when his sinus rate rose above 95 bpm, he developed Mobitz type 1, second-degree heart block and shortly thereafter developed 2:1 heart block (Fig. 34.2, top middle panel). His blood pressure remained stable and he denied any symptoms when the heart block developed. He was therefore allowed to continue to exercise. He eventually stopped exercising due to leg fatigue. His ventricular rate at peak exercise was only 81 bpm (with an atrial rate of 162 bpm). During recovery, 1:1 conduction returned once his sinus rate fell below 110 bpm. His oxygen pulse at peak exercise was supranormal. His $\dot{V}_E/\dot{V}_{CO2}$ slope was high and his end-tidal pCO_2 during exercise was

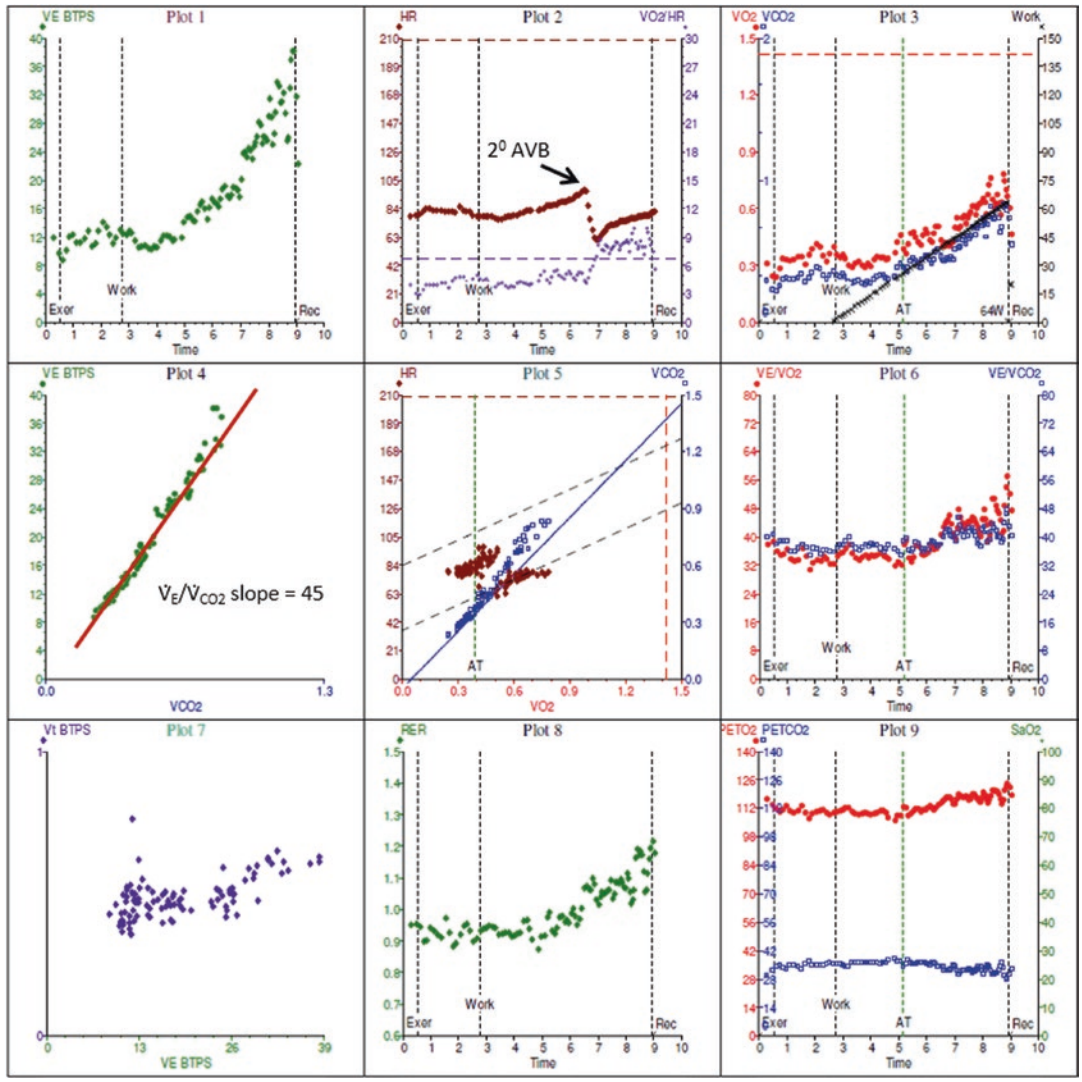


Fig. 34.2 Nine-panel graph of data from cardiopulmonary exercise test from patient 34.2: hypoplastic left heart syndrome, s/p Fontan, second-degree heart block

low. His arterial oxygen saturation remained within normal limits throughout the study.

In this case, the patient's poor exercise function was due primarily to the second-degree heart block and the consequent abnormal chronotropic response to exercise. He was able to partially compensate for the chronotropic deficit by increasing his stroke volume (as reflected by his oxygen pulse) to above normal values, probably as a result of the Starling mechanism. However, even with the increased stroke volume, he could not fully compensate for the profound bradycardia at higher levels of exercise, and his aerobic function was quite low, even for a patient with a Fontan circulation. The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 were probably the result of the ventilation/perfusion mismatch and consequent inefficient gas exchange commonly encountered in Fontan patients.

It is notable that this patient denied exercise intolerance. This phenomenon is likely attributable to the fact that, having been born with severe

cyanotic congenital heart disease, he had never known what it is like to have a normal heart. It is also unclear how longstanding the second-degree heart block might have been. The fact that he was asymptomatic and did not acknowledge any recent deterioration in exercise function suggests that it had not developed recently.

Case 34.3: Complex/Failing Fontan

The patient was a 36-year-old man who was born with a hypoplastic left ventricle, mitral atresia, and ventricular septal defect. He underwent initial pulmonary artery banding, coarctation repair, and atrial septectomy when he was an infant, followed by a classic Glenn shunt (i.e., superior vena cava to right pulmonary artery) when he was 6 years old. At 11 years of age, he underwent a modified Fontan procedure in which his inferior vena cava was baffled to his left pulmonary artery. A Damus–Kaye–Stansel procedure and subaortic resection were also performed at that time. He subsequently developed sinus node dysfunction and received an epicardial atrial pacemaker. He also was known to have developed pulmonary arteriovenous malformations (AVMs) in his right lung (a common complication of classic Glenn shunts). In addition, he struggled with protein-losing enteropathy, venous stasis disease in his lower extremities, and recurrent atrial arrhythmias. At the time of his evaluation, however, he denied shortness of breath, chest pain, palpitations, paroxysmal nocturnal dyspnea, and orthopnea. Although he was able to work as a computer programmer, he led a very sedentary lifestyle and engaged in very little physical activity. He was maintained on digoxin, amiodarone, furosemide, and aspirin. His echocardiogram revealed good ventricular function and only mild valvular insufficiency. A cardiopulmonary exercise test (Table 34.3 and Fig. 34.3) was undertaken to further characterize his current clinical status.

The test was performed on a cycle ergometer using a 20 W/min ramp. His peak respiratory exchange ratio was 1.26, indicating that he expended a good effort. His peak work rate, peak $\dot{V}_{O2}$, and $\dot{V}_{O2}$ at the ventilatory anaerobic threshold were severely depressed. His oxygen pulse at peak exercise was also severely depressed. His heart rate increased excessively for his level of $\dot{V}_{O2}$ during exercise, and his peak heart rate was normal. His $\dot{V}_E/\dot{V}_{CO2}$ slope was elevated and his end-tidal pCO_2 during exercise was abnormally low. His rhythm was atrially paced at rest. Sinus rhythm emerged during exercise. Occasional atrial premature beats were detected, especially near peak exercise. No more complex ectopy was seen. His baseline oxygen saturation was 81%, and it rose to 86% at peak exercise.

Table 34.3 Patient 34.3: complex/failing Fontan. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	16.1
Peak $\dot{V}_{O2}$ (%predicted)	42
Peak work rate (W)	117
Peak work rate (%predicted)	54
Peak RER	1.26
Peak O_2 pulse (%predicted)	47
Peak heart rate (bpm)	150
Peak heart rate (%predicted)	88
Heart rate increase	Excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	23
End-tidal pCO_2 at VAT (mm Hg)	33
End-tidal pCO_2 during exercise	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	37
Baseline spirometry	Mild restrictive pattern
Tidal volume at peak exercise (%FVC)	50
Respiratory rate at peak exercise (breaths/min)	34
Breathing reserve (%)	46
Rhythm	A-paced →sinus, frequent PACs
Blood pressure response	Blunted
Oxygen saturation at rest (%)	81
Oxygen saturation at peak exercise (%)	86

This patient presented with the clinical picture of failing Fontan physiology. This picture was affirmed by the exercise test. The factor primarily responsible for his poor exercise function was an inability to increase his effective stroke volume (as reflected by the low oxygen pulse at peak exercise) during exercise. The relatively mild

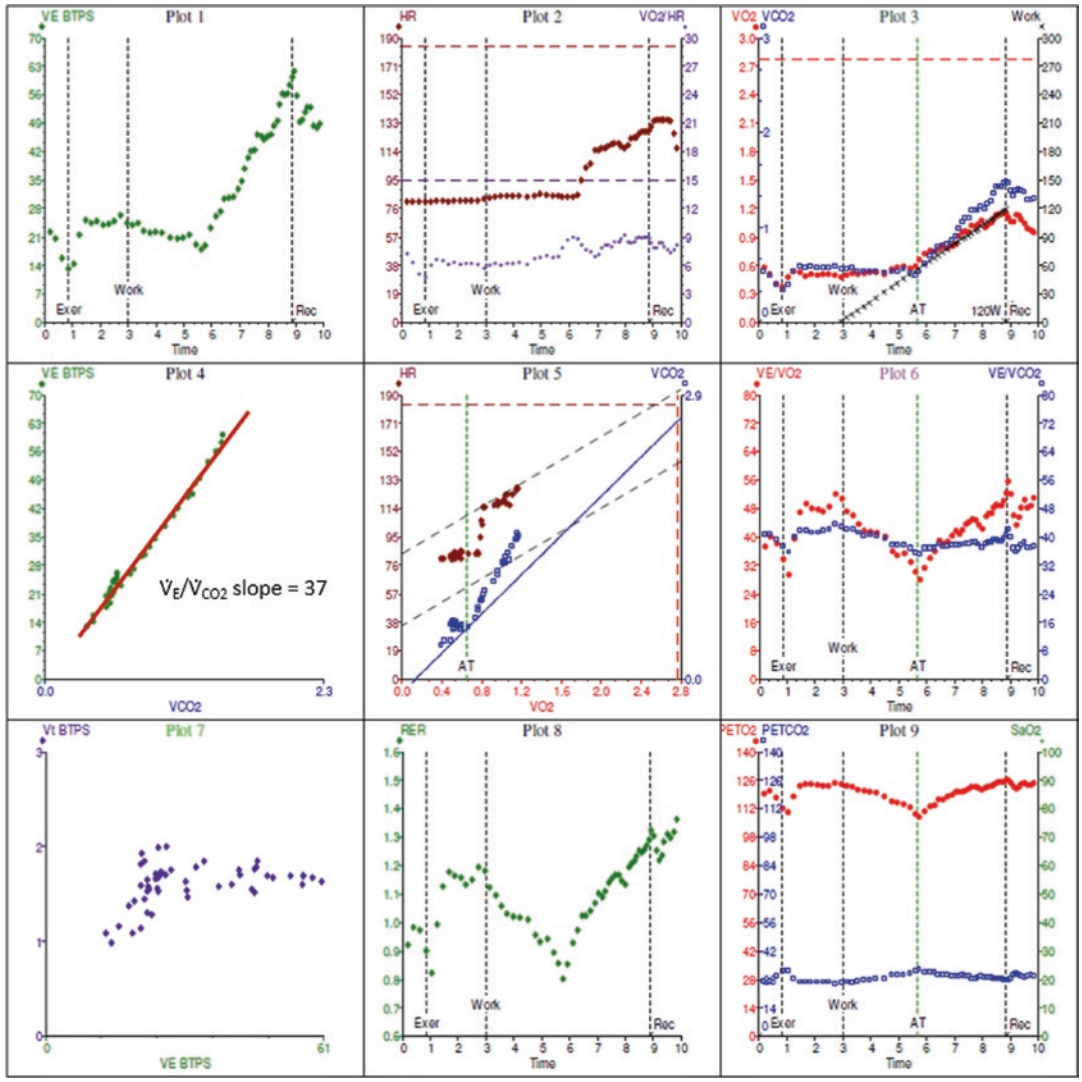


Fig. 34.3 Nine-panel graph of data from cardiopulmonary exercise test from patient 34.3: complex/failing Fontan

arterial desaturation at peak exercise probably made only a minor contribution to the low peak-exercise oxygen pulse. The discrepancy between his exercise function (in particular his peak $\dot{V}_{O2}$ and oxygen pulse) and his echocardiographic findings once again illustrates the fact that for many Fontan patients, the factor limiting exercise function is not the cardiac function but (probably) the pulmonary vascular function.

The elevated $\dot{V}_E/\dot{V}_{CO2}$ and low end-tidal pCO_2 are typical of patients with Fontan physiology and were probably due, to a large extent, to the pulmonary blood flow maldistribution and consequent ventilation/perfusion mismatch that results from the absence of pulsatile pulmonary blood flow. The pulmonary AVMs and associated physiologic right-to-left shunting also contributed to these abnormal findings. The increase in oxygen saturation during exercise was quite unusual, however. This phenomenon probably reflected the fact that cycle exercise disproportionately increased the blood flow to, and venous return from, the lower extremities. The patient's surgically modified anatomy caused this venous return

to be selectively directed to the patient's left lung (i.e., the lung without pulmonary AVMs). Consequently, the saturation of the *mixture* of blood returning from his lungs (and then being pumped to his body) was higher than it was at rest.

Case 34.4: A 1.5 Ventricle Repair

The patient was a 12-year-old girl who was born with critical pulmonic stenosis with an intact ventricular septum and a hypoplastic right ventricle (RV) and tricuspid valve. She underwent a balloon valvuloplasty procedure at 2 days of age. She remained cyanotic and prostaglandin dependent following this procedure and therefore underwent surgical implantation of a 3.5 mm right Blalock–Taussig shunt and ligation of the ductus arteriosus when she was 6 days old. When she was 10 months old, she underwent surgical takedown of the Blalock–Taussig shunt, a bidirectional Glenn procedure (division of the superior vena cava and end-to-side anastomosis of the distal end of the superior venacava to the right pulmonary artery), restriction of the atrial septum, a tricuspid valvuloplasty, and resection of RV muscle bundles, due to progressive cyanosis and ongoing hypoplasia of the RV and tricuspid hypoplasia/stenosis. Right ventricle to pulmonary artery continuity was left intact. She did well following this procedure, and it was possible to electively close the residual atrial septal communication in the cardiac catheterization laboratory when she was 4 years old. Her subsequent clinical course was uneventful.

At the time of her exercise test, she was asymptomatic and denied exercise intolerance. Her physical examination was remarkable only for a 2/6 systolic ejection murmur at the left upper sternal border. Her echocardiogram revealed mild pulmonary regurgitation and no pulmonary stenosis. The tricuspid valve remained moderately hypoplastic, but there was no diastolic gradient across the valve and there was only trivial tricuspid regurgitation. The right atrium was dilated but no residual atrial communication was detected. The RV remained mildly hypoplastic. The bidirectional Glenn shunt was patent and unobstructed. A CPET was obtained (Table 34.4 and Fig. 34.4) to further characterize her current cardiologic status.

Table 34.4 Patient 34.4: 1.5 ventricle repair. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	25.0
Peak $\dot{V}_{O2}$ (%predicted)	82
Peak work rate (W)	90
Peak work rate (%predicted)	98
Peak RER	1.15
Peak O_2 pulse (%predicted)	86
Peak heart rate (bpm)	184
Peak heart rate (%predicted)	95
Heart rate increase	Slightly excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	42
End-tidal pCO_2 at VAT (mm Hg)	34
End-tidal pCO_2 during exercise	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	32
Forced vital capacity (%predicted)	89
FEV1 (%predicted)	93
FEF 25–75 (%predicted)	115
Breathing reserve (%)	49
Rhythm	Sinus throughout study
Blood pressure response	Normal
Oxygen saturation at rest (%)	96
Oxygen saturation at peak exercise (%)	96

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold, *FEV1* Volume exhaled in the first second of forced expiration, *FEF* forced expiratory flow

The test was performed on a cycle ergometer with an 18 W/min ramp. Her respiratory exchange ratio at peak exercise was 1.15, indicating that she expended an adequate effort. Her peak work rate and peak heart rate were normal. The heart rate increase was slightly excessive for the level of $\dot{V}_{O2}$ during exercise (Fig. 34.4, middle panel). Her peak $\dot{V}_{O2}$ and oxygen pulse were in the low-normal/borderline-depressed range. Her $\dot{V}_E/\dot{V}_{CO2}$ slope was elevated and her end-tidal pCO_2 during exercise was low (Fig. 34.4, left middle panel and right lower panel, respectively). No significant arterial desaturation was detected.

The borderline depression of the peak $\dot{V}_{O2}$ and oxygen pulse probably reflected the fact that the persistently hypoplastic RV, burdened by its

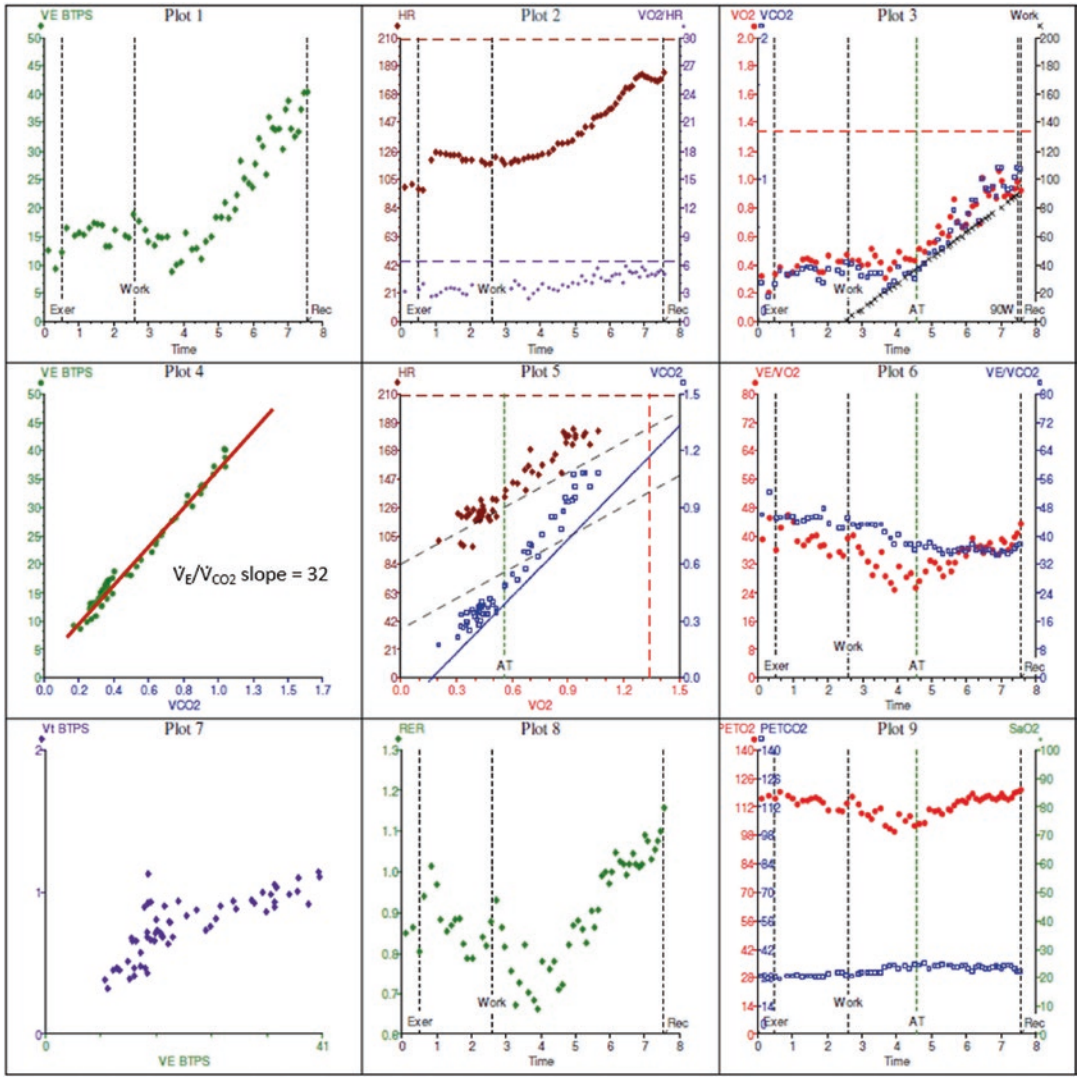


Fig. 34.4 –Nine-panel graph of data from cardiopulmonary exercise test from patient 34.4: 1.5 ventricle repair

hypoplastic tricuspid valve, was unable to augment forward stroke volume adequately during exercise. The heart rate increased excessively during exercise to compensate for the stroke volume deficit. The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 probably reflected the fact that pulmonary blood flow maldistribution and ventilation/perfusion mismatch were present in this patient with a bidirectional Glenn and a 1.5 ventricle repair, in a manner analogous to that seen in most patients with Fontan physiology (see Chap. 15).

Case 34.5: Corrected Transposition with Second-Degree AV Block

The patient was a 35-year-old man with {I,D,D} transposition of the great arteries (corrected transposition in the setting of situs inversus) with a ventricular septal defect (VSD) and subpulmonary stenosis. He had undergone surgical repair of his VSD and resection of the subpulmonary stenosis when he was 12 years old. He had been doing well following this surgery, with mild residual subpulmonary and branch pulmonary artery stenosis,

Table 34.5 Patient 34.5: corrected transposition with second-degree AV block. Selected data from cardiopulmonary exercise test

Parameter	Pre-pacemaker	Post-pacemaker
Peak $\dot{V}_{O2}$ (ml/kg/min)	21.0	24.3
Peak $\dot{V}_{O2}$ (%predicted)	55	73
Endurance time (min)	6:00	9:15
Endurance time (%ile)	<10th	25–50th
Peak RER	1.15	1.14
Peak O_2 pulse (%predicted)	117	87
Peak heart rate (bpm)	87	151
Peak heart rate (%predicted)	47	84
Heart rate increase	Severely depressed	Mildly depressed
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	37	46
End-tidal pCO_2 at VAT (mm Hg)	35	36
End-tidal pCO_2 during exercise	Low	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	35	36
Breathing reserve (%)	58	44
Rhythm	Sinus→2:1 AV block	A-sensed/V-paced
Blood pressure response	Normal	Normal

until several months prior to his exercise test, when he began to notice decreased exercise tolerance. A cardiopulmonary exercise test (Table 34.5) was performed to further evaluate his symptoms.

The patient achieved a peak respiratory exchange ratio of 1.15, indicating an adequate effort was expended. Despite his good effort, his peak $\dot{V}_{O2}$ and endurance time were quite low. His anaerobic threshold was also depressed. At rest, the patient was in a sinus-like rhythm with 1:1 AV conduction. About 20 s after the initiation of exercise, at a sinus rate of 110 bpm, he developed Mobitz type I second-degree AV block, which progressed to 2:1 block as exercise continued. His ventricular rate at peak exercise was therefore quite low (87 bpm). His oxygen pulse at peak exercise was high (117%predicted). Normal AV conduction returned in recovery.

The results of the CPET indicated that the patient's profound chronotropic insufficiency, due to the second-degree AV block, was the primary factor responsible for his exercise intolerance. (AV node dysfunction is common in patients with atrioventricular discordance.) The low ventricular rate did allow more time for ventricular filling and permitted the ventricle to move up its Starling curve. The stroke volume (reflected by the oxygen pulse at peak exercise) was therefore supranormal. This adaptation partially compensated for the chronotropic defect (his exercise function would have been even worse without it). The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 were probably the result of ventilation/perfusion mismatch secondary to residual pulmonary artery stenoses. The high breathing reserve reflected the fact that the patient's cardiovascular problems limited his ability to increase his metabolic rate.

Following the exercise test, the patient underwent implantation of a transvenous dual chamber pacemaker. A subsequent exercise test (Table 34.5) revealed substantial improvements in endurance time and peak $\dot{V}_{O2}$, associated with a much more normal chronotropic response to exercise and a much higher (near normal) peak heart rate. His rhythm during exercise was predominantly A-sensed/V-paced (pacemaker-mediated Wenckebach developed near peak exercise). With the higher peak heart rate, the oxygen pulse (and presumably the stroke volume at peak exercise) declined to the low-normal range. This change probably reflected the fact that the higher ventricular rate resulted in a shorter period for ventricular filling and unmasked a mild degree of systemic ventricular dysfunction related to the presence of a systemic right ventricle.

It is instructive to compare this patient to the patient from Case 33.6 (see Chap. 33). The indication for pacemaker implantation in this case was profound bradycardia during exercise due to second-degree AV block. It is therefore not surprising that the pacemaker produced a substantial improvement in exercise function. In contrast, the indication for pacemaker implantation in Case 33.6 was profound bradycardia at rest and concern regarding the patient's risk for Stokes–Adams attacks, mitral valve deterioration, and cardiac arrest. In fact, that patient's chronotropic response to exercise was only mildly depressed. Moreover, that patient had a structurally normal heart and was more capable of increasing her

stroke volume to compensate for her chronotropic insufficiency. Consequently, the pacemaker had a much smaller impact upon her exercise function.

Case 34.6: l-TGA with Heart Block

The patient was a young man who was born with l-transposition of the great arteries (TGA) and high-grade AV block. He remained asymptomatic throughout childhood, adolescence, and early adulthood. He never required an intervention. At an evaluation when he was 28 years old, he reported that he was able to run a 10 K race and was training to run a marathon. A cardiac magnetic resonance image (MRI) revealed good ventricular function and only mild systemic (tricuspid) AV valve regurgitation. A cardiopulmonary exercise test at that time (Table 34.6 and Fig. 34.5a) revealed that his exercise capacity was good. His gas exchange during exercise was normal. Although he had second-degree AV block with junctional escape beats at rest, he developed 1:1 conduction (with first-degree AV block) with exercise. His peak heart rate was low, consistent with a degree of coexistent sinus node dysfunction, but he was able to compensate for this chrontropic defect by increasing his stroke volume (as reflected by his oxygen pulse) to supranormal levels. Second-degree AV block returned during recovery.

He continued to do well thereafter, without significant symptoms. Over the years, however, he did not (or could not) exercise as much as he had in the past. A repeat CPET at age 35 (Table 34.6 and Fig. 34.5b) revealed that his peak exercise parameters had deteriorated significantly and that he now had complete heart block with a ventricular escape rhythm. Although his peak heart rate was similar to that present on his previous study, no evidence of AV conduction was detected. The robust compensatory increase in stroke volume present on the previous exercise test was not observed. Indeed, the oxygen pulse at peak exercise was significantly depressed, despite the low peak heart rate. His $\dot{V}_E/\dot{V}_{CO2}$ slope had become quite elevated and his end-tidal pCO_2 during exercise was low. Of note, a repeat cardiac MRI revealed no significant change in his ventricular function, although the tricuspid regurgitation had worsened somewhat.

Following this CPET, a dual-chamber rate-modulated (DDDR) pacemaker was implanted. A CPET was performed following this procedure (Table 34.6 and Fig. 34.5c) and revealed significant improvement in his peak exercise parameters. His gas exchange during exercise had normalized. His rhythm was A-paced/V-paced throughout the study, and his peak heart rate was normal. The oxygen pulse at peak exercise was higher than it had been on the previous study, despite the substantially higher peak heart rate.

Table 34.6 Patient 34.6: l-TGA with heart block. Selected data from cardiopulmonary exercise tests (CPETs)

Parameter	CPET 1	CPET 2	CPET 3
Peak $\dot{V}_{O2}$ (ml/kg/min)	31.7	15.3	24.7
Peak $\dot{V}_{O2}$ (%predicted)	83	40	65
Peak work rate (W)	252	203	239
Peak work rate (%predicted)	92	70	84
Peak RER	1.14	1.13	1.18
Peak O_2 pulse (ml/beat)	23.1	11.9	13.2
Peak O_2 pulse (%predicted)	119	57	63
Peak heart rate (bpm)	123	121	176
Peak heart rate (%predicted)	69	71	104
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	41	26	30
End-tidal pCO_2 at VAT (mm Hg)	42	26	45
$\dot{V}_E/\dot{V}_{CO2}$ slope	23	42	26
End-tidal pCO_2 during exercise	Normal	Low	Normal
Rhythm	2^0 AVB→1^0 AVB	CHB; ventricular escape rhythm	A-paced/V-paced
Blood pressure response	Normal	Normal	Normal

The heart rate during exercise was in fact somewhat elevated for the level of oxygen consumption during exercise.

The decline in exercise function between the first and second exercise tests, despite the similar peak heart rates, probably reflected the loss of AV synchrony and consequent decline in stroke volume, as well as the time-related decline in tricuspid valve and systemic right ventricular function (not readily detectable on MRI studies at rest) that is often encountered in patients with l-transposition. The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 on the second study were probably the result of ventilation/perfusion mismatch secondary to left atrial hypertension that resulted from the loss of AV synchrony as well as the ventricular dysfunction and tricuspid regurgitation. The improvement in exercise function following the pacemaker implantation was probably the result of the more physiologic heart rate response to exercise, as well as a better stroke volume response to exercise following the restoration of AV synchrony. These favorable physiologic changes also probably reduced the left atrial hypertension during exercise and thereby reduced V/Q mismatch and improved gas exchange. The peak oxygen pulse did not return to normal, however, because a degree of tricuspid and right (systemic) ventricular dysfunction probably persisted.

a

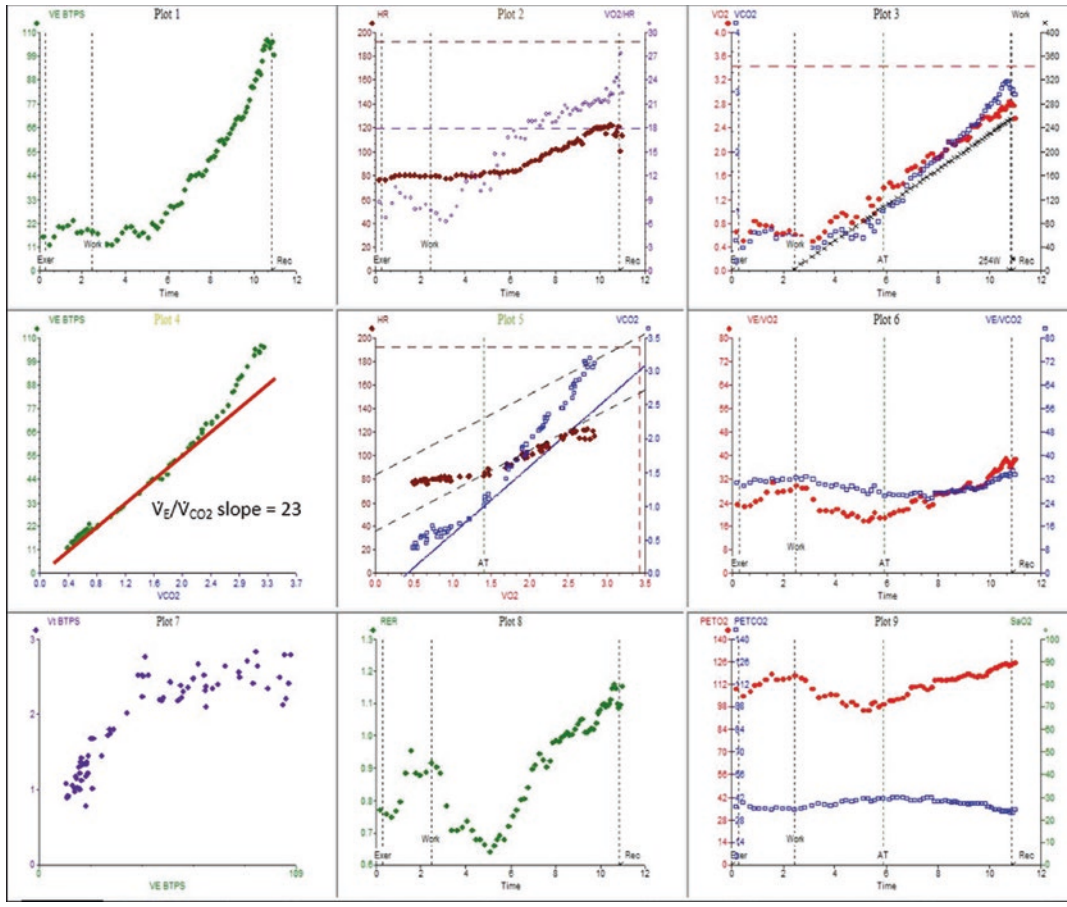


Fig. 34.5 (**a**) At age 28, a nine-panel graph of data from cardiopulmonary exercise test from patient 34.6: l-TGA with heart block. (**b**) Repeat of test at age 35. (**c**) CPET following implantation of DDDR pacemaker

b

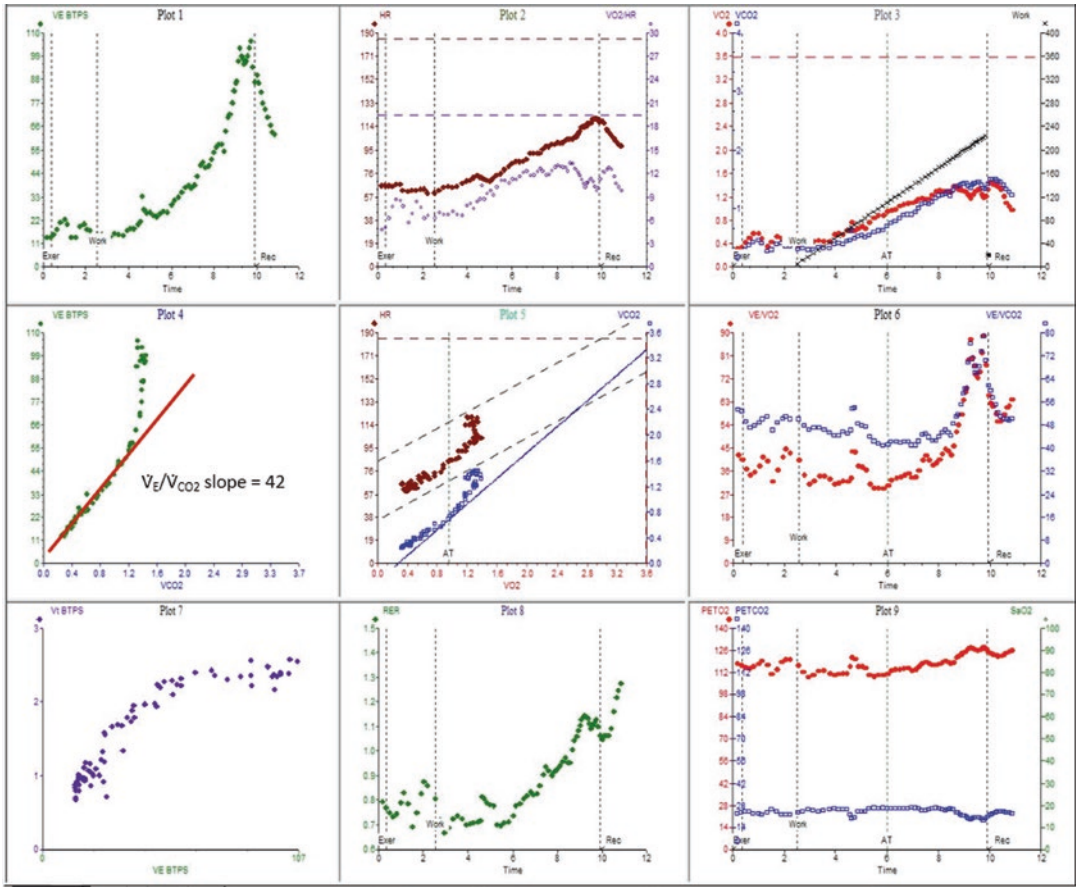


Fig. 34.5 (continued)

c

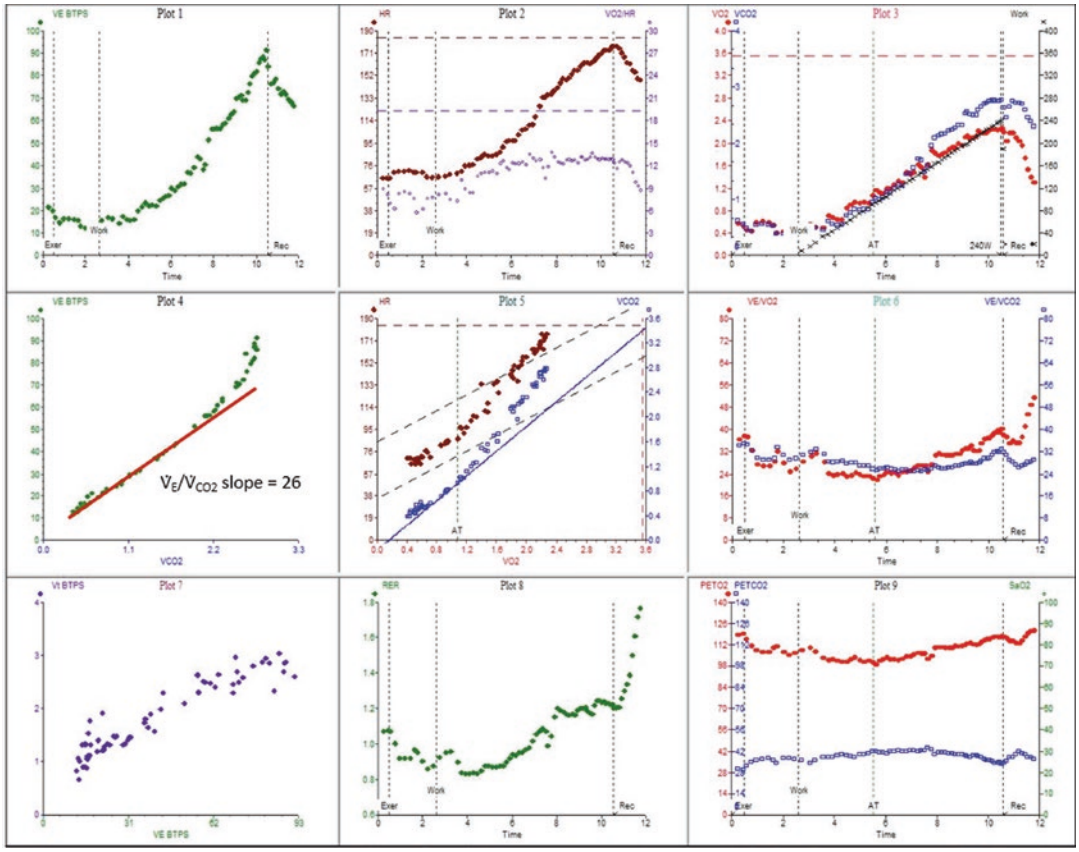


Fig. 34.5 (continued)

This case also illustrates once again that patients often do not recognize (or subconsciously deny) a gradual decline in exercise function. These changes are readily appreciated on formal CPET, however.

Case 34.7: d-TGA, s/p Atrial Switch, and Progressive Right Ventricular Dysfunction

The patient was a 32-year-old man with d-transposition of the great arteries. Initially, he was palliated with a balloon atrial septostomy. Other medical problems (necrotizing enterocolitis and multi-organ system failure) had made him a poor candidate for a neonatal arterial switch. A two-stage arterial switch strategy was therefore pursued, and he underwent a pulmonary artery band and Blalock–Taussig shunt to "prepare" his left ventricle when he was 5 months old. One year later, he was brought to the operating room for an arterial switch procedure. However, in the operating room, he was found to have an intramural coronary artery. Because of this unfavorable coronary artery anatomy, an atrial switch (Senning) procedure (with take down of the pulmonary artery band and Blalock–Taussig shunt) was performed instead. Postoperatively, he had markedly depressed systemic RV function and a degree of systemic tricuspid valve regurgitation. When he was 11 years old, he developed high-

grade atrioventricular block and underwent implantation of a DDDR pacemaker.

Despite this complicated history, he did surprisingly well during childhood and adolescence. As an adult, he was able to work full-time. He claimed to be asymptomatic and worked out regularly at a gym. He was maintained on carvedilol, enalapril, and aspirin. His echocardiogram continued to demonstrate severe right ventricular dysfunction as well as moderate tricuspid regurgitation (perhaps slightly worse than on his previous study 17 months earlier). His mean dP/dt during isovolumetric contraction (an index of ventricular systolic function that is independent of anatomic or geometric factors [1, 2]) fell from 397 mm Hg/s to 340 mm Hg/s. A CPET was obtained to further assess his current cardiopulmonary status (Table 34.7 and Fig. 34.6). A cycle ergometer with a 20 W/min ramp was employed.

Despite achieving an adequate RER at peak exercise, his peak $\dot{V}_{O2}$, work rate, heart rate, and oxygen pulse were all quite low. The $\dot{V}_{O2}$ at the VAT was also low. He had an elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and a low end-tidal pCO2 during exercise. His breathing reserve at peak exercise was high. His baseline spirometry revealed a mild obstructive pattern at rest, which worsened slightly post-exercise. His peak $\dot{V}_{O2}$ had declined 28% and his peak work rate had declined 15% compared to a study obtained 17 months earlier. The decline was associated with a 26% decline in his peak-exercise oxygen pulse. His peak heart rate was similar (96 vs. 98 bpm). His $\dot{V}_E/\dot{V}_{CO2}$ slope was 6% higher.

The patient's poor exercise function was due to a combination of chronotropic impairment (probably related to the beta-blocker therapy ± the intrinsic sinus node dysfunction commonly encountered in patients who have had atrial switch procedures) and right (systemic) ventricular dysfunction. In the presence of the significant chronotropic defect, the patient should have had a supranormal stroke volume at peak exercise. Hence, the magnitude of the stroke volume deficiency was even worse than that conveyed by the oxygen pulse data. The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope may have been due to inefficient gas exchange secondary to elevated pulmonary venous pressure and/or pulmonary blood flow maldistribution related to subtle pulmonary venous baffle obstruction. Although the patient also had coexistent obstructive lung disease, the substantial breathing reserve at peak exercise indicated that his exercise function was not limited by respiratory factors.

The CPET also revealed a significant deterioration in exercise function that, based upon the decline in the oxygen pulse, appeared to be due to a decline in his stroke volume response to exercise. This decline could not be appreciated on the basis of the patient's symptomatology or on the basis of qualitative echocardiographic assessments of his baseline right ventricular function

Table 34.7 Patient 34.7: d-TGA, s/p atrial switch, and progressive right ventricular dysfunction. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	16.2
Peak $\dot{V}_{O2}$ (%predicted)	39
Peak work rate (W)	125
Peak work rate (%predicted)	57
Peak RER	1.24
Peak O_2 pulse (%predicted)	71
Peak heart rate (bpm)	96
Peak heart rate (%predicted)	55
Peak respiratory rate (breaths/min)	35
Peak tidal volume (%FVC)	38
Breathing reserve (%)	52[a]
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	23
End-tidal pCO_2 at peak exercise (mm Hg)	30
$\dot{V}_E/\dot{V}_{CO2}$ slope	38
Pre-forced vital capacity (%predicted)	88
Pre-FEV1 (%predicted)	77
Pre-FEV1/FVC (%)	72
Pre-FEF 25–75 (%predicted)	55
Post-forced vital capacity (%predicted)	91
Post-FEV1 (%predicted)	72
Post-FEV1/FVC (%)	66
Post-FEF 25–75 (%predicted)	48
Baseline arterial O_2 saturation (%)	98
Peak-exercise arterial O_2 saturation (%)	97
Rhythm	A-sensed/V-paced
Blood pressure response	Blunted

[a]Based on post-exercise spirometric measurements

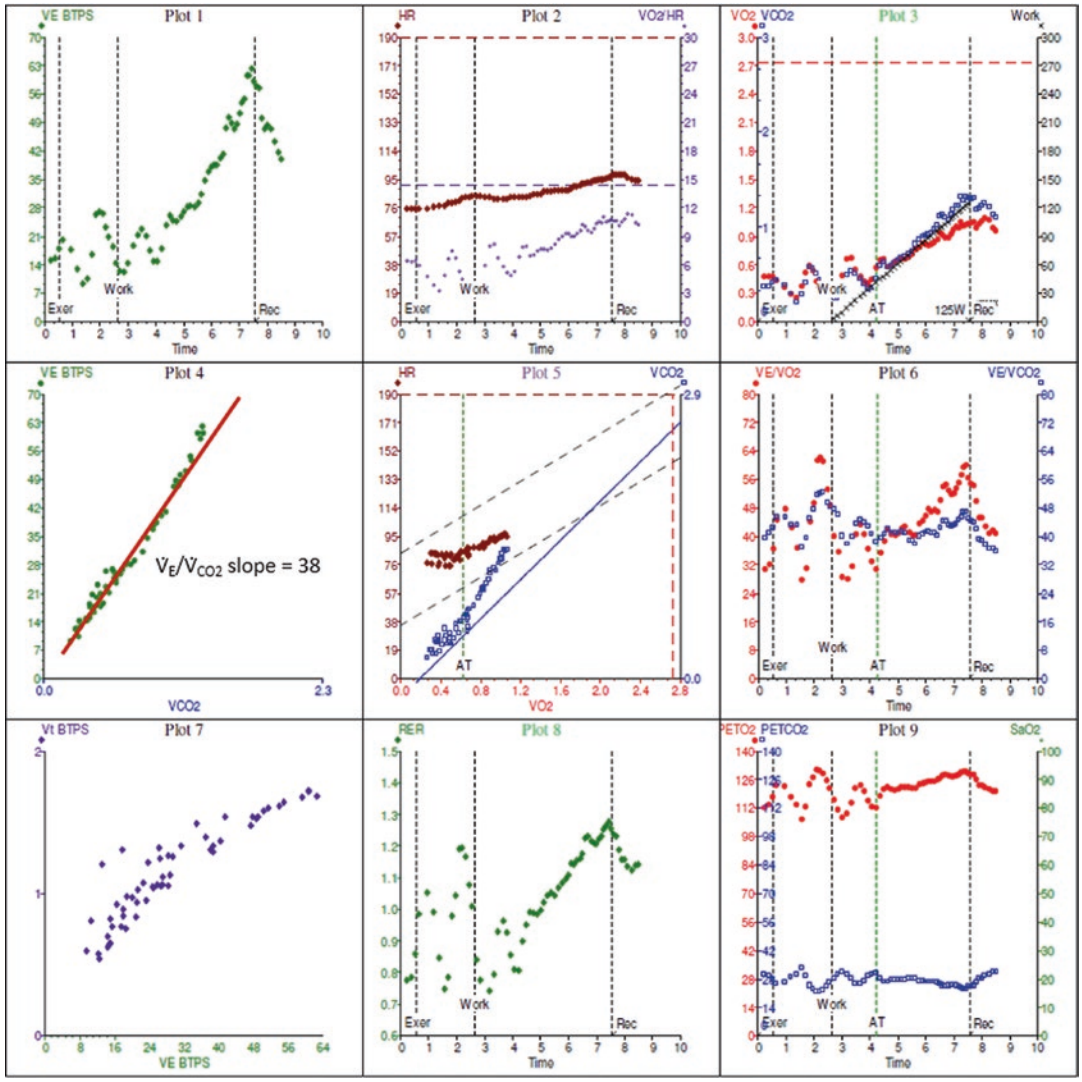


Fig. 34.6 Nine-panel graph of data from cardiopulmonary exercise test from patient 34.7: d-TGA, s/p atrial switch, progressive right ventricular dysfunction

(which were limited on account of the patient's complex anatomy and poor echocardiographic windows). It was associated with a significant decline in the mean dP/dt during isovolumetric contraction as well as slight (qualitative) worsening of the tricuspid insufficiency, findings that suggest that the systemic right ventricle's systolic function had indeed declined over the past 17 months.

Case 34.8: Tricuspid Atresia and s/p Bidirectional Glenn Shunt

The patient was a 40-year-old woman who was born with tricuspid atresia type 1B (small ventricular septal defect with normally related great arteries). Over the course of her life, she had undergone multiple palliative surgical procedures. Two attempts to complete a Fontan palliation were

unsuccessful due to prohibitively high pulmonary artery pressures. At the time of her evaluation, her pulmonary blood flow was provided by a bidirectional Glenn shunt and a 6 mm Gore–Tex shunt between the aorta and the superior vena cava. In the 6 years that had elapsed since the construction of the latter shunt, however, it had become almost completely obstructed. She also had a history of sinus node dysfunction palliated with a dual-chamber epicardial pacemaker. Despite these serious cardiovascular issues, the patient nevertheless claimed to be relatively asymptomatic (New York Heart Association [NYHA] Class II). A cardiopulmonary exercise test was obtained to further asses her current status (Table 34.8 and Fig. 34.7). At the time of her exercise test, her hemoglobin was 19.9 g/dl and hematocrit was 61.8%. Her echocardiographic windows were limited but her ventricular function was thought to be normal.

A cycle ergometer with a 10 W/min ramp was used for the CPET. The test revealed severely depressed aerobic function, despite achieving an adequate RER. Both the peak heart rate and the oxygen pulse at peak exercise were low. The arterial oxygen saturation, which was low at rest, declined precipitously with exercise. The $\dot{V}_E/\dot{V}_{CO2}$ slope was quite high and the end-tidal pCO_2 during exercise was quite low.

Table 34.8 Patient 34.8: tricuspid atresia and s/p bidirectional Glenn shunt. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	8.7
Peak $\dot{V}_{O2}$ (%predicted)	32
Peak work rate (W)	45
Peak work rate (%predicted)	26
Peak RER	1.17
Peak O_2 pulse (%predicted)	54
Peak heart rate (bpm)	97
Peak heart rate (%predicted)	58
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	26
End-tidal pCO_2 at VAT (mm Hg)	29
End-tidal pCO_2 during exercise	Very low
$\dot{V}_E/\dot{V}_{CO2}$ slope	56
Rhythm	Sinus
Blood pressure response	Blunted
Oxygen saturation at rest (%)	75
Oxygen saturation at peak exercise (%)	58
Forced vital capacity (%predicted)	44
FEV1 (%predicted)	38
FEV1/FVC (%)	86
FEF 25–75 (%predicted)	24
Breathing reserve (%)	25

The low peak heart rate reflected the patient's sinus node dysfunction—a condition commonly encountered among patients who have had a bidirectional Glenn procedure. The precipitous decline in oxygen saturation probably can be explained by the fact that cycling disproportionately increases the blood flow to the lower extremities and the venous return from the lower extremities to the inferior vena cava. In this patient, the inferior vena caval return shunted right to left across the atrial septum, where it mixed with the blood returning from the lungs. The flow to the lungs, however, was derived almost exclusively from the bidirectional Glenn shunt, which drained the venous blood from the head and upper body. Blood flow to these areas does not increase much during lower extremity exercise. Hence, during exercise, deoxygenated blood returning from the lower extremities comprised a progressively greater proportion of the blood entering the left atrium (and thereafter, the left ventricle and aorta). Moreover, the saturation of the blood returning from the exercising muscles in the lower extremities was lower during exercise, as the muscles extracted a greater percentage of oxygen from the blood during exercise.

Several factors may have accounted for the low oxygen pulse at peak exercise, the most important of which was probably the profound arterial desaturation. This physiologic abnormality was partially mitigated, however, by the patient's elevated hemoglobin. It is hard to know to what degree a low stroke volume may have contributed to the low oxygen pulse. Given the normal baseline LV function, and the fact that increased venous return from the lower extremities was able to flow unimpeded to the LV, it is possible that the increase in forward stroke volume during exercise was relatively normal. However, increasing the stroke volume with deoxygenated blood will not increase the oxygen pulse (see Chap. 11). In this case, it is better to think of the oxygen pulse as the amount of oxygen added to the blood with each heart beat (see

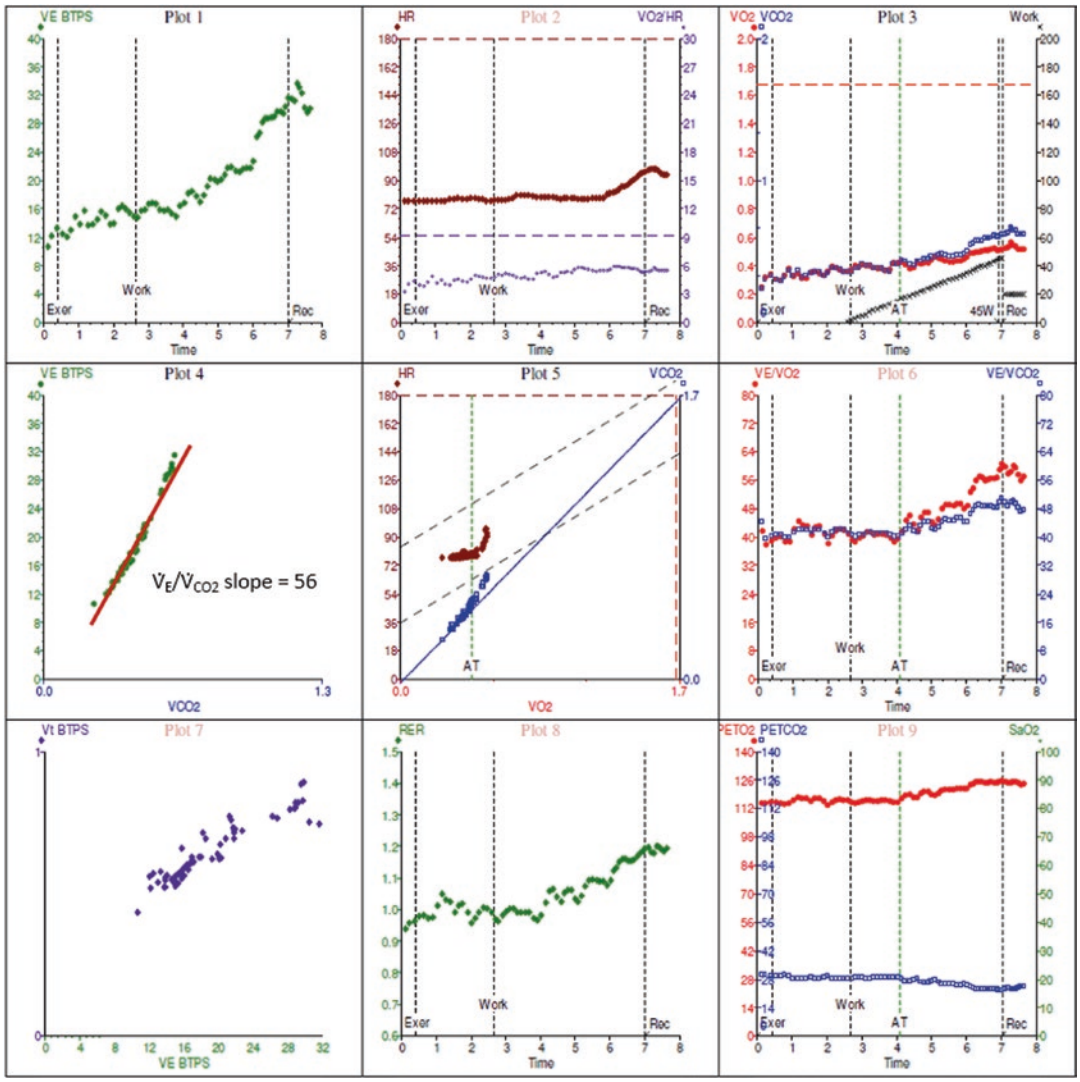


Fig. 34.7 Nine-panel graph of data from cardiopulmonary exercise test from patient 34.8: tricuspid atresia, s/p bidirectional Glenn shunt

Chap. 15). With that conceptual framework, one can appreciate that, in this patient, because the blood flow to the lungs does not increase significantly during lower extremity exercise, the oxygen pulse at peak exercise (which is closely related to pulmonary blood flow divided by heart rate at peak exercise) is also depressed.

The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 were the result of the obligate right-to-left shunting associated with this patient's anatomy. Ventilation/perfusion mismatch secondary to pulmonary blood flow maldistribution and/or pulmonary arteriovenous malformations (which commonly develop in patients with bidirectional Glenn shunts) may also have contributed to these anomalies.

Based upon the spirometric measurements, this patient also had significant restrictive/obstructive lung disease. This phenomenon is common among patients with congenital heart disease, especially those who have undergone multiple surgical procedures. The patient's

breathing reserve at peak exercise (25%) suggests, however, that her exercise capacity was not limited by her lung disease.

Case 34.9: Complex Cyanotic Congenital Heart Disease/Single Ventricle Physiology

The patient was a 46-year-old man with complex cyanotic congenital heart disease (double inlet left ventricle, dextrocardia, severe valvar, and subvalvar pulmonic stenosis) who had been palliated with a classic right Blalock–Taussig shunt when he was 7 years old. He had been managed conservatively since then. At the time of his visit, he had no cardiopulmonary symptoms. He worked full-time at an automobile dealership and exercised at a gym on a regular basis. He felt that there had been no recent decline in his exercise capacity. His only medication was low-dose aspirin. His echocardiogram revealed the previously described anatomy. The ventricular function was good. There was only mild atrioventricular valve insufficiency. There was severe, multilevel pulmonic stenosis with a maximum instantaneous gradient of 105 mm Hg. The Blalock–Taussig shunt was patent. His hemoglobin at the time of the visit was 16.0 g/dl, with normal red blood cell indices. A CPET (Table 34.9 and Fig. 34.8) was performed to further assess his current cardiopulmonary status. A cycle ergometer with a 20 W/min ramp was employed for the study. Exercise was terminated due to shortness of breath.

The respiratory exchange ratio at peak exercise was 1.09, indicating that he expended an adequate effort and that exercise was terminated near his cardiovascular limit. His peak $\dot{V}_{O2}$ and peak work rate were moderately-severely depressed. The $\dot{V}_{O2}$ was also quite low. An inability to augment the oxygen pulse appropriately during exercise appeared to be the primary factor responsible for these abnormalities. The ability to increase heart rate during exercise was fairly well preserved. His (left arm) blood pressure response to exercise was normal. His baseline oxygen saturation was low (85%) and declined progressively during exercise, reaching a nadir of 70%. His $\dot{V}_E/\dot{V}_{CO2}$ slope was quite elevated and his end-tidal pCO_2 during exercise was quite low. A mild-moderate obstructive pattern was present on his baseline spirometry, but his breathing reserve at peak exercise was 32%.

Table 34.9 Patient 34.9: complex cyanotic congenital heart disease/single ventricle physiology. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	19.4
Peak $\dot{V}_{O2}$ (%predicted)	55
Peak work rate (W)	115
Peak work rate (%predicted)	61
Peak RER	9.3
Peak O_2 pulse (%predicted)	65
Peak heart rate (bpm)	137
Peak heart rate (%predicted)	85
Heart rate increase	Slightly excessive
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	28
End-tidal pCO_2 at VAT (mm Hg)	24
End-tidal pCO_2 during exercise	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	53
Rhythm	Ectopic atrial
Blood pressure response (left arm)	Normal
Oxygen saturation at rest (%)	85
Oxygen saturation at peak exercise (%)	70
Forced vital capacity (%predicted)	79
FEV1 (%predicted)	74
FEF 25–75 (%predicted)	57
Breathing Reserve (%)	32

The patient's low oxygen pulse at peak exercise was to a large extent due to his severe arterial desaturation during exercise. In this case, the typical relationship between the oxygen pulse and the effective stroke volume was distorted by the low arterial oxygen saturation (and consequent low arterial oxygen content; see Chap. 11). Under these circumstances, the oxygen pulse underestimates the stroke volume. The polycythemia (reflected by the elevated hemoglobin level) partially compensated for the arterial desaturation and distorted the relationship between the oxygen pulse and effective stroke volume in the opposite direction. However, in this case, the polycythemia was mild compared to the desaturation. With this complex physiology, it is hard to know to what extent an inability to increase the effective stroke volume during exercise may have contributed to the low oxygen pulse and poor exercise function; the magnitude of the arterial

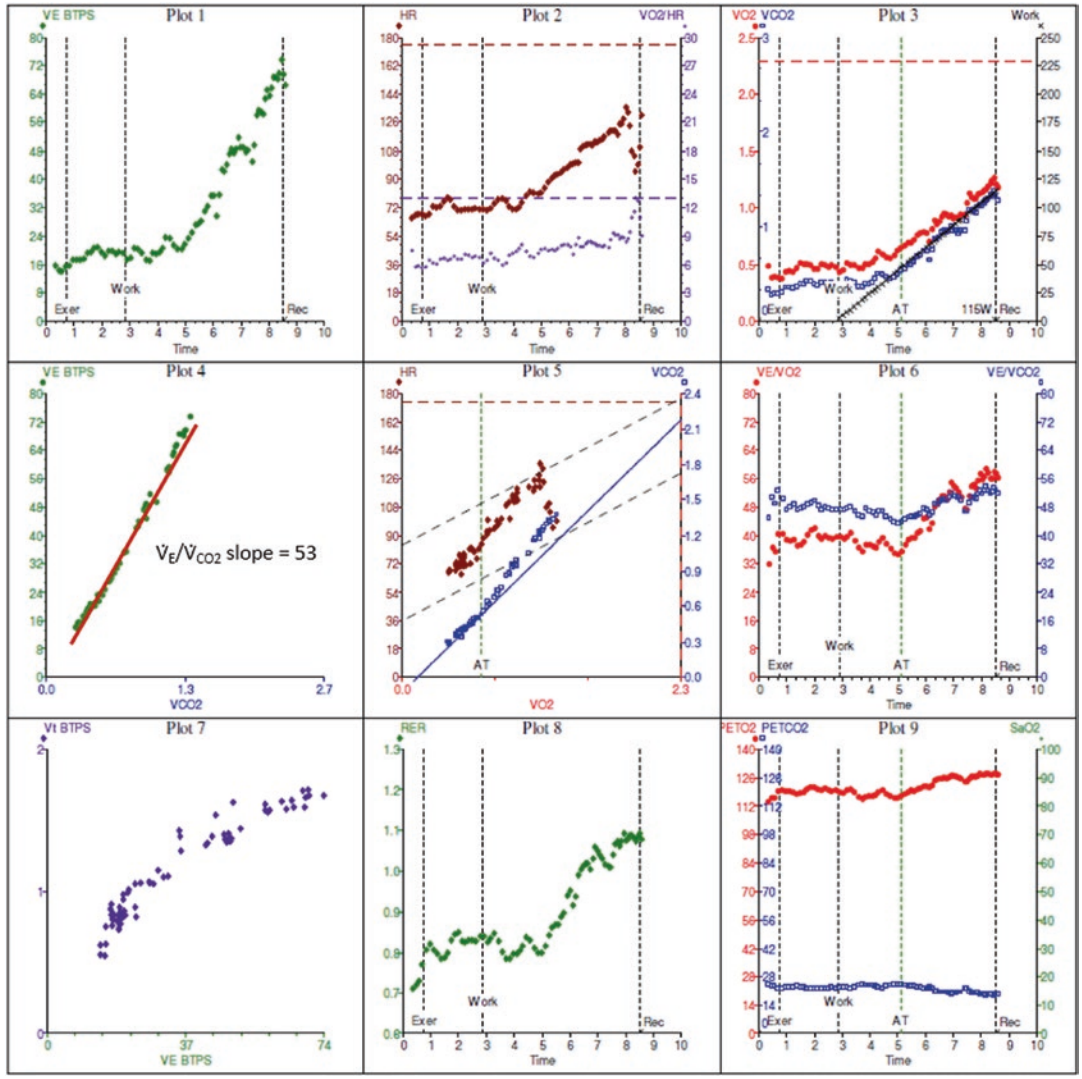


Fig. 34.8 Nine-panel graph of data from cardiopulmonary exercise test from patient 34.9: complex cyanotic congenital heart disease/single ventricle physiology

desaturation and oxygen pulse depression suggest that this was a relatively minor factor.

Two factors probably account for the progressive arterial oxygen desaturation. First, the amount of blood that could flow to the lungs across the stenotic pulmonary outflow tract and Blalock–Taussig shunt was probably relatively fixed. During exercise, however, the increase in ventricular contractility and decrease in systemic vascular resistance caused the systemic blood flow to increase. Hence, the pulmonary-to-systemic blood flow ratio decreased and the right-to-left shunting increased during exercise. The second factor responsible for the progressive arterial desaturation was the increased oxygen extraction that accompanied exercise. On account of this phenomenon, the blood shunting right to left had a lower saturation, and the arterial oxygen saturation (which in this single ventricle, total mixing lesion is the saturation that results from the mixing of the blood returning from the body with the blood returning from the lungs) was lower for any given level of right-to-left shunting.

The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope (Fig. 34.8, left middle panel) and low end-tidal pCO_2 (Fig. 34.8, right lower panel) were likely due to the obligate right-to-left intracardiac shunting that resulted from the patient's single ventricle (complete mixing) physiology (see Chap. 12). However, despite the inefficient ventilation that resulted from the patient's cyanotic congenital heart disease, and the pulmonary disease identified on baseline spirometry, the patient's ample breathing reserve at peak exercise indicates that exercise was terminated on account of cardiovascular (i.e., an inability to deliver sufficient quantities of oxygen to the exercising muscles) rather than respiratory factors.

It is also interesting to note that this exceptional patient claimed to be asymptomatic, despite the severe physiologic abnormalities and functional deficits that were so apparent on the exercise test. This phenomenon is probably due to the fact that he had never known what it is like to exercise with a normal heart.

Case 34.10: Unrepaired Cyanotic Congenital Heart Disease

The patient was a 26-year-old man with heterotaxy syndrome and complex cyanotic congenital heart disease (asplenia, double outlet right ventricle, pulmonic stenosis, unbalanced, RV dominant complete AV canal defect, hypoplastic left ventricle, common atrium, and complex venous anatomy). He had undergone a left modified Blalock–Taussig shunt when he was 6 months old and several subsequent cardiac catheterizations for left pulmonary artery stenosis and/or shunt obstruction. For personal reasons, he had refused to undergo further surgical palliative procedures. At the time of his exercise test, he reported low but stable exercise tolerance. He was able to work 4 hours twice a week, delivering pizza. He could not climb more than one flight of stairs without resting. He was maintained only on amoxicillin and vitamin D supplementation. His hemoglobin was 19.7 g/dl and hematocrit 66.9. An exercise test (Table 34.10 and Fig. 34.9) was obtained to further characterize his current cardiopulmonary status. The test was performed on a cycle ergometer with a 10 W/min ramp.

Table 34.10 Patient 34.10: unrepaired cyanotic congenital heart disease. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	12.2
Peak $\dot{V}_{O2}$ (%predicted)	33
Peak work rate (W)	46
Peak work rate (%predicted)	29
Peak RER	1.11
Peak O_2 pulse (%predicted)	45
Peak heart rate (bpm)	131
Peak heart rate (%predicted)	73
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	20
End-tidal pCO_2 during exercise	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	75
Forced vital capacity (%predicted)	91
FEV1 (%predicted)	89
FEF 25–75 (%predicted)	89
Breathing reserve (%)	63
Rhythm	Sinus with occasional premature ventricular contractions
Blood pressure response	Low-normal
Oxygen saturation at rest (%)	77
Oxygen saturation at peak exercise (%)	61

The patient's oxygen saturation at rest was 77% and fell to 61% at peak exercise. His respiratory exchange ratio near peak exercise was 1.11. His peak work rate and peak $\dot{V}_{O2}$ were very low. The ventilatory anaerobic threshold was also quite low and appeared to occur during unloaded cycling. The oxygen pulse at peak exercise was extremely low. His peak heart rate was also depressed, but the heart rate increase, relative to his $\dot{V}_{O2}$ during exercise, was excessively rapid. The $\dot{V}_E/\dot{V}_{CO2}$ slope was extremely high and the end-tidal pCO_2 during exercise was quite low. His spirometric measurements were relatively normal and his breathing reserve was high.

The respiratory exchange ratio of 1.11 suggests that the patient expended an adequate effort. His low oxygen pulse at peak exercise was probably due to his profound arterial desaturation as well as an inability to augment his forward stroke volume normally. His polycythemia probably only partially compensated for his arterial desaturation. In this case, the low arterial oxygen saturation and the elevated hemoglobin confound the

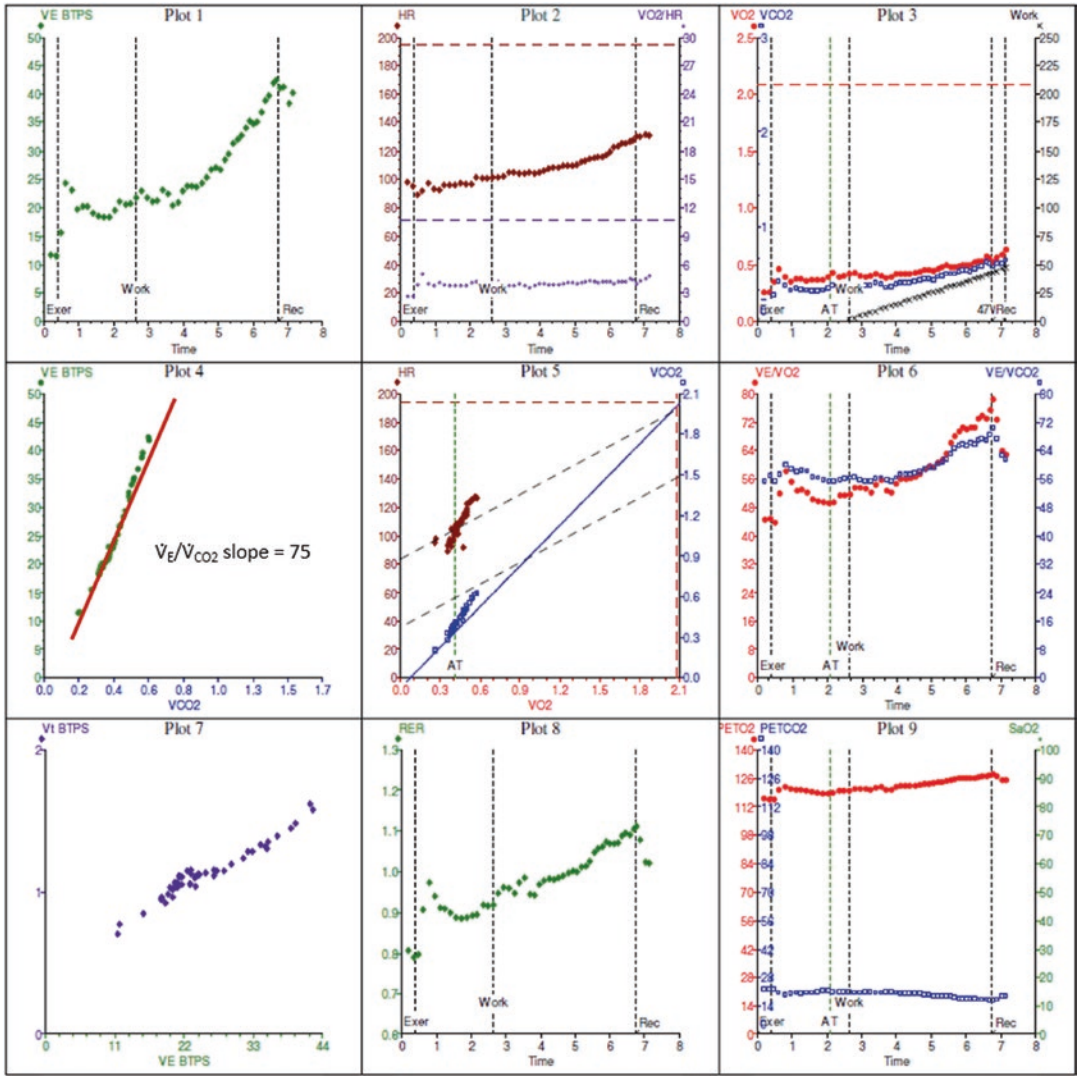


Fig. 34.9 Nine-panel graph of data from cardiopulmonary exercise test from patient 34.10: unrepaired cyanotic congenital heart disease

typical relationship between the oxygen pulse and effective stroke volume at peak exercise (see Chap. 11). It is therefore hard to know exactly how severe the patient's stroke volume depression actually was. It is likely, however, that both the low oxygen saturation and the lower-than-normal effective stroke volume combined to limit oxygen delivery and hence $\dot{V}_{O2}$ during exercise. The low peak heart rate may reflect the sinus node dysfunction commonly encountered among patients with heterotaxy syndromes and may also have contributed to the patients' poor exercise function. However, the excessive rise in heart rate during exercise (Fig. 34.9, middle panel) was likely an autonomic response to the low oxygen delivery during exercise. The excessive ventilation (Fig. 34.9, left middle panel) and low end-tidal pCO_2 (Fig. 34.9, right lower panel) during exercise were probably a result of the right-to-left shunting, as well as a degree of ventilation/perfusion mismatch (see Chap. 12).

The decline in the patient's arterial oxygen saturation during exercise probably was a result of 2 phenomena:

1. The patient's pulmonary blood flow was relatively limited and fixed by the resistance across his Blalock–Taussig shunt and native pulmonary outflow tract, whereas the increased contractility, increased heart rate, pumping action of the skeletal muscles, and decreased systemic vascular resistance combined to cause his systemic blood flow to increase (see Chap. 2). Hence, the pulmonary-to-systemic blood flow ratio declined during exercise.
2. The decline in mixed venous oxygen saturation secondary to increased oxygen extraction during exercise caused the blood that was shunting right to left to have a lower saturation during exercise.

The low anaerobic threshold reflected the fact that the patient's ability to provide oxygen to his exercising muscles was impaired. They therefore developed an early and excessive reliance upon anaerobic metabolism to generate the ATP required for exercise. The high breathing reserve reflected the fact that the patient's congenital heart disease could not support a high metabolic rate.

Case 34.11: Cyanotic Congenital Heart Disease, Pre- and Postsurgical Repair

The patient was a 15-year-old female who had been followed with the diagnoses of LV noncompaction with mild-to-moderate ventricular dysfunction, apical ventricular septal defect (VSD), secundum atrial septal defect (ASD), mildly hypoplastic atypical right ventricle, and valvar pulmonic stenosis. As a child, her hemodynamics were fairly "balanced" and she was "asymptomatic." Surgical intervention was thought to carry a high risk and medical therapy was therefore recommended. However, over the years, she became more and more symptomatic. At the time of her evaluation, she could climb no more than one flight of stairs before stopping to catch a breath. She was able to walk on flat terrain for ~20 min and would "turn blue" with this amount of activity. A cardiac catheterization revealed a cardiac index of 2.5 l/min/m^2 with an aortic saturation of 77%, mixed venous saturation of 58%, normal pulmonary venous saturation, and hemoglobin of 18.8 g/dl. There was severe pulmonic stenosis with right-to-left shunting across the VSD (and ASD). Her pulmonary-to-systemic blood flow ratio (Q_p/Q_s) was 0.6. Her mean right and left atrial pressures were 8–9 mm Hg. Her right ventricular pressure was systemic. There was a 75 mm Hg gradient between the right ventricle and main pulmonary artery. The pulmonary artery pressure was 21/14 with a mean of 17 mm Hg. Angiography revealed primarily valvar pulmonic stenosis and right-to-left shunting across the large apical VSD. The RV and LV function appeared mildly depressed. Her cardiopulmonary exercise test data are summarized in Table 34.11 and Fig. 34.10a. The study was performed on a cycle ergometer with a 10 W/min ramp.

Table 34.11 Patient 34.11: cyanotic congenital heart disease, pre- and postsurgical repair. Selected data from cardiopulmonary exercise tests

Parameter	Pre-Op	Post-Op
Peak $\dot{V}_{O2}$ (ml/kg/min)	14.0	20.5
Peak $\dot{V}_{O2}$ (%predicted)	52	87
Peak work rate (W)	61	102
Peak work rate (%predicted)	58	98
Peak RER	1.10	1.12
Peak O_2 pulse (ml/beat)	5.6	9.1
Peak O_2 pulse (%predicted)	74	108
Peak heart rate (bpm)	146	153
Peak heart rate (%predicted)	71	81
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	38	46
End-tidal pCO_2 at VAT (mm Hg)	28	34
End-tidal pCO_2 during exercise	Low	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	55	30
Forced vital capacity (%predicted)	88	80
FEV1 (%predicted)	73	67
FEF 25–75 (%predicted)	45	38
Breathing reserve (%)	35	29
Rhythm	Sinus, rare PVC	Sinus, rare PVC
Blood pressure response	Normal	Normal
Oxygen saturation at rest (%)	77	91
Oxygen saturation at peak exercise (%)	57	83

PVC premature ventricular contractions. All other abbreviations as for Table 34.1

a

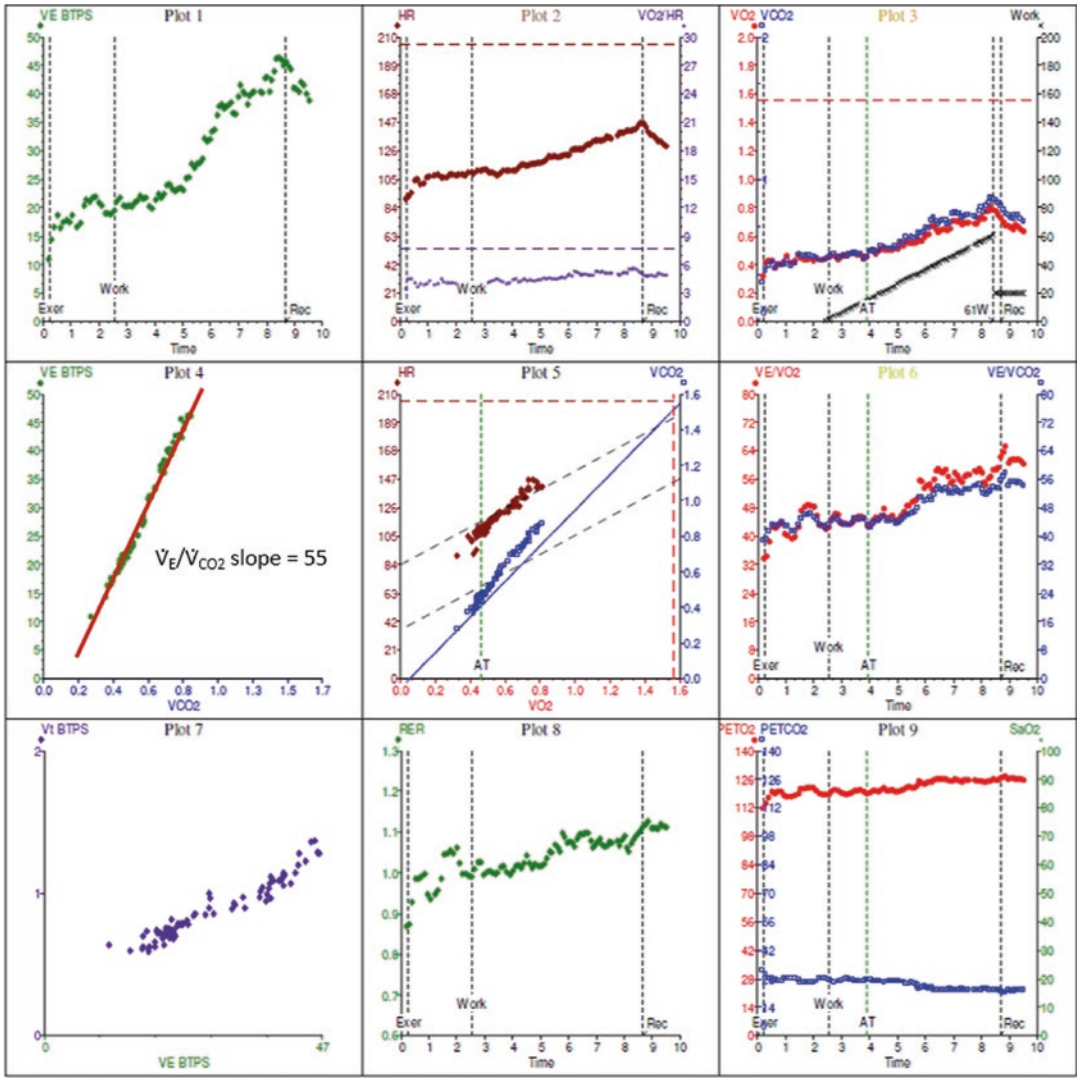


Fig. 34.10 (**a**) Nine-panel graph of data from cardiopulmonary exercise test from patient 34.11: cyanotic congenital heart disease, pre- and postsurgical repair. (**b**) CPET following surgical pulmonary valvotomy and repair of her apical VSD and secundum ASD

b

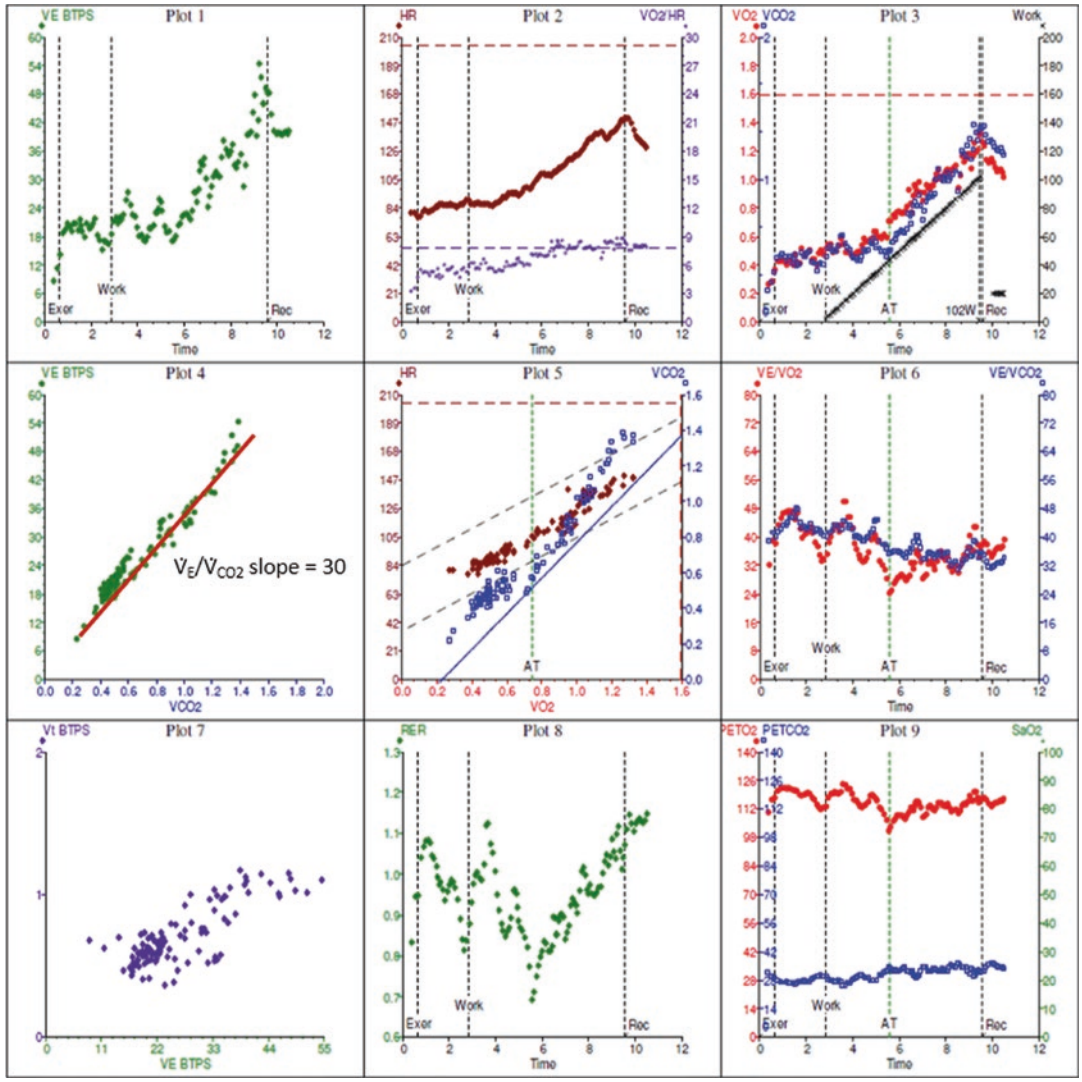


Fig. 34.10 (continued)

Her peak respiratory exchange ratio was 1.10, indicating that she expended an adequate effort. Her peak work rate and peak $\dot{V}_{O2}$ were very low. The ventilatory anaerobic threshold and oxygen pulse at peak exercise were also low. Her peak heart rate was mildly depressed, but the heart rate increase, relative to her $\dot{V}_{O2}$ during exercise, was normal. Her oxygen saturation at rest was 77% and fell progressively during exercise to a nadir of 57% at peak exercise. The $\dot{V}_E/\dot{V}_{CO2}$ slope was extremely high and the end-tidal pCO_2 during exercise was quite low. Her spirometric measurements revealed a moderate obstructive pattern, but her breathing reserve at peak exercise was normal.

As in previously presented cases of unrepaired cyanotic congenital heart disease, the decline in the patient's arterial oxygen saturation during exercise probably was a result of two phenomena:

1. A further decline in her Q_p/Q_s ratio because her pulmonary blood flow was relatively fixed on account of her severe valvar pulmonic stenosis (with this physiology, the exercise-induced decline in pulmonary arteriolar resistance will have a minimal impact upon pulmonary blood flow), while the increased contractility, increased heart rate, pumping action of the skeletal muscles, and decreased systemic vascular resistance combined to cause her systemic blood flow to increase (see Chap. 2).
2. The decline in mixed venous oxygen saturation that occurs secondary to increased oxygen extraction during exercise. This phenomenon caused the blood that was shunting right to left to have a lower saturation during exercise (compared to rest).

The right-to-left shunting was also responsible for the elevated $\dot{V}_E/\dot{V}_{CO2}$ slope (Fig. 34.10a, left middle panel), and the low end-tidal pCO_2 (Fig. 34.10a, right lower panel) during exercise was probably a result of the right-to-left shunting (see Chap. 12). The low oxygen pulse at peak exercise was due largely to the low arterial oxygen saturation (although this factor was partially mitigated by the patient's elevated hemoglobin). A low effective stroke volume at peak exercise may also have contributed to this phenomenon. The low peak-exercise heart rate may have been due to a degree of sinus node dysfunction. Although this patient's baseline spirometry revealed the presence of some obstructive lung disease, the ample breathing reserve at peak exercise indicated that respiratory factors were not responsible for her exercise intolerance.

Following this evaluation, the patient underwent surgical pulmonary valvotomy and repair of her apical VSD and secundum ASD. She did well postoperatively but was noted to have persistent arterial desaturation. Subsequent echocardiograms and cardiac catheterization studies revealed right-to-left shunting across a previously unrecognized, partially unroofed coronary sinus (coronary sinus septal defect). No other residual shunts were detected. She also had moderate LV dysfunction and moderate tricuspid insufficiency. Her symptoms, however, were dramatically improved. She was able to jog about a mile without stopping and had begun to play softball. Another cardiopulmonary exercise test (Table 34.11 and Fig. 34.10b) was performed to further evaluate her clinical status. On this study, her respiratory exchange ratio was 1.12, indicating that she expended an adequate effort. Her peak work rate, peak $\dot{V}_{O2}$, and $\dot{V}_{O2}$ at the ventilatory anaerobic threshold were dramatically improved. Although her peak heart rate remained somewhat depressed, her peak oxygen pulse was now supranormal (despite her baseline ventricular dysfunction), indicating that she was able to compensate for her chrontropic defect by increasing the forward stroke volume (via the Starling mechanism) during exercise. She now had only mild arterial desaturation at rest secondary to the right-to-left shunting across her partially unroofed coronary sinus. (The tricuspid regurgitation and the mild RV hypoplasia caused this atrial level shunt to be predominantly right to left.) Her saturation fell further with exercise probably on account of increased oxygen extraction as well as an increase in the right-to-left shunting. The $\dot{V}_E/\dot{V}_{CO2}$ slope (Fig. 34.10a, b, left middle panel) remained high, and the end-tidal pCO_2 (Fig. 34.10a, b, right lower panel) remained low, probably as a consequence of the residual right-to-left shunting. However, they were much improved compared to pre-op. She continued to have evidence of obstructive lung disease on her baseline spirometry, but her substantial breathing reserve at peak exercise indicated that her exercise tolerance was not limited by respiratory factors.

Nineteen months transpired between the two exercise tests and the patient gained 9.8 kg during this time period.

Case 34.12: d-TGA, VSD, Eisenmenger's Syndrome, and s/p Palliative Mustard Procedure

The patient was a 48-year-old man who was born with d-transposition of the great arteries with a large ventricular septal defect (VSD). He did not have any surgical interventions when he was a young infant. A cardiac catheterization at 5 months of age documented severe pulmonary vascular obstructive disease (Eisenmenger's syndrome).

On account of progressive cyanosis, he underwent a surgical atrial septectomy (Blalock–Hanlon procedure) when he was 5 years old and a palliative atrial switch (Mustard) procedure when he was 11 years old. The VSD was left open. He subsequently did fairly well until age 32, when he developed atrial flutter. This arrhythmia was controlled with amiodarone and digoxin. At age 36, he was hospitalized for management of congestive heart failure. He responded well to this therapy. At age 43, he underwent an ablation procedure for recurrent atrial flutter. This intervention was partially successful. At the time of his visit, he was able to walk on flat terrain without difficulty but would become short of breath with more intense physical activity. He also would note fluid retention when he consumed too much salt. A cardiac MRI revealed moderate biventricular dysfunction (ejection fractions ~42%). His pulmonary:systemic blood flow ratio (Qp/Qs) was estimated to be 1.2. His hemoglobin was 16.2 and hematocrit 47. His other medications included furosemide, metoprolol, thyroid replacement hormone, and coumadin. He was referred for a cardiopulmonary exercise test to further characterize his current cardiopulmonary status (Table 34.12 and Fig. 34.11).

Table 34.12 Patient 34.12: d-TGA, VSD, Eisenmenger's syndrome, and s/p palliative Mustard procedure. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	9.4
Peak $\dot{V}_{O2}$ (%predicted)	29
Peak work rate (W)	71
Peak work rate (%predicted)	35
Peak RER	1.31
Peak O_2 pulse (%predicted)	73
Peak heart rate (bpm)	63
Peak heart rate (%predicted)	40
Heart rate increase	Depressed
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	23
End-tidal pCO_2 at VAT (mm Hg)	33
End-tidal pCO_2 during exercise	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	42
Rhythm	Sinus, rare APC
Blood pressure response	Blunted
Oxygen saturation at rest (%)	92
Oxygen saturation at peak exercise (%)	72
Forced vital capacity (%predicted)	54
FEV1 (%predicted)	56
FEV1/FVC	86
FEF 25–75 (%predicted)	76
Breathing reserve (%)	40

The CPET was performed on a cycle ergometer with a 12 W/min ramp. The respiratory exchange ratio at peak exercise was 1.31, indicating that a good effort was expended. The patient's peak work rate, peak $\dot{V}_{O2}$, peak heart rate, and $\dot{V}_{O2}$ at the VAT were all severely depressed. The oxygen pulse at peak exercise was depressed to a more modest degree. Mild arterial oxygen desaturation was present at rest. The arterial oxygen saturation fell substantially during exercise. The $\dot{V}_E/\dot{V}_{CO2}$ slope was quite elevated and the end-tidal pCO_2 during exercise was low. The blood pressure response was blunted.

The patient's low exercise capacity was due to a number of factors. He had severe chronotropic insufficiency, probably as a result of the amiodarone and beta-blocker therapy. Given his history, he also may have had a component of underlying sinus node dysfunction. In addition, the severe arterial oxygen desaturation impaired oxygen delivery to his muscles during exercise. The decline in oxygen saturation was due to the fact that his pulmonary vascular resistance was relatively fixed. Hence, as he exercised and his systemic vascular resistance fell, he began to shunt more and more blood right to left across his VSD and his Qp/Qs declined. Increased peripheral oxygen extraction and consequent lower mixed venous oxygen saturation also contributed to this phenomenon. The elevated hemoglobin partially compensated for the low oxygen saturation. The low oxygen pulse at peak exercise was probably due primarily to the arterial desaturation, rather than a low stroke volume, although it is hard to be certain on account of all of the confounding factors present in this case. However, the compensatory increase in stroke volume, expected in the presence of the severe chronotropic defect, almost certainly was not present. Consequently, ventricular dysfunction also probably contributed to his exercise intolerance. The elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and low end-tidal pCO_2 were due to the right-to-left shunting as well as ventilation/perfusion mismatch that accompanies pulmonary vascular obstructive disease. Based on his spirometric measurements, the patient also had a degree of restrictive lung disease. This observation is not

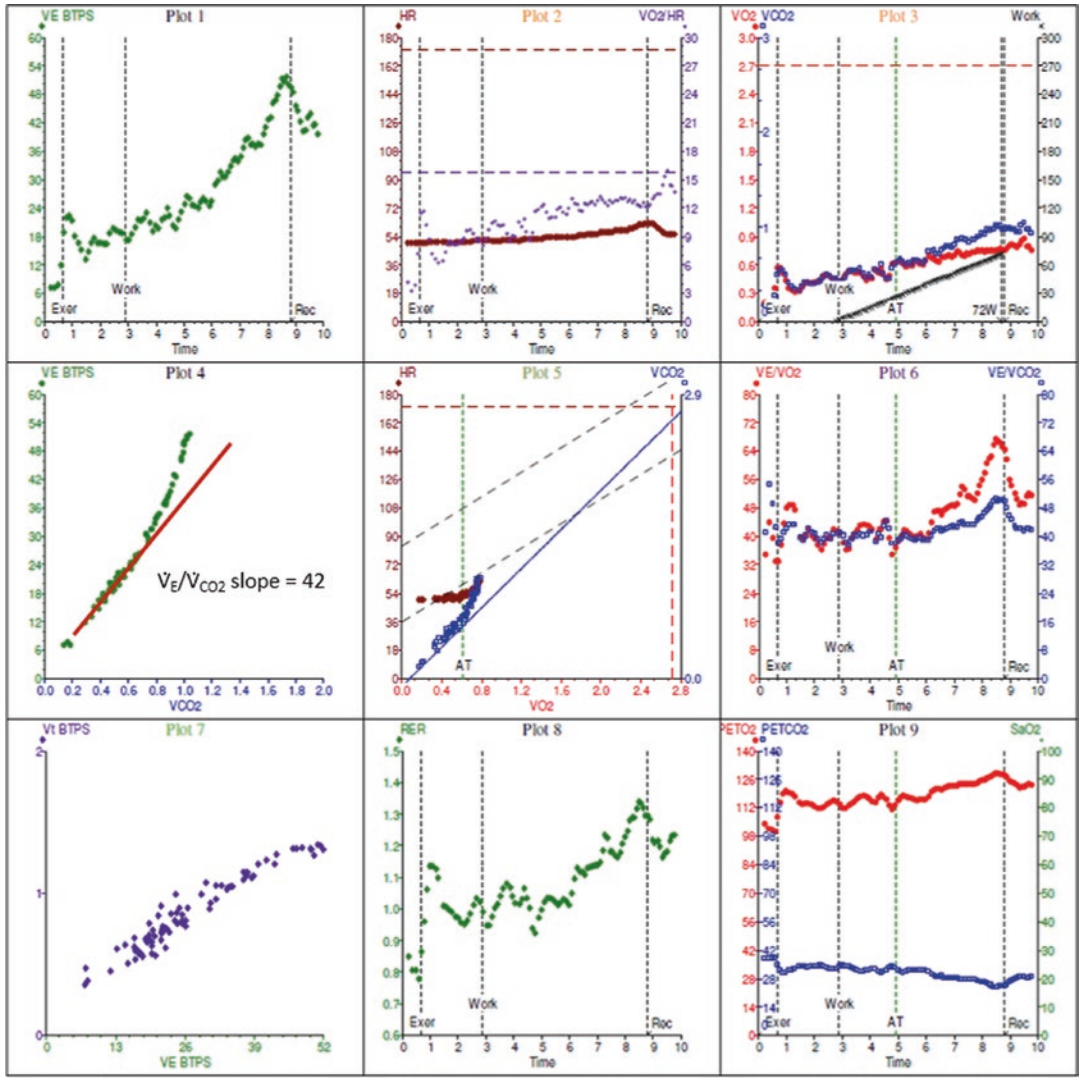


Fig. 34.11 Nine-panel graph of data from cardiopulmonary exercise test from patient 34.12: d-TGA, VSD, Eisenmenger's syndrome, s/p palliative Mustard procedure

surprising in light of the patient's medical and surgical history. The ample breathing reserve at peak exercise indicates, however, that his exercise capacity was not limited by respiratory issues.

Case 34.13: Physiology of an Unusual Right-to-Left Shunting

The patient was a 7-year-old boy with a persistent left superior vena cava (LSVC) that drained into his left atrium. Aside from mild cyanosis, he was completely asymptomatic. An exercise test was obtained to further assess his cardiopulmonary function. The test was performed on a treadmill, as he was too small for the cycle ergometer. A Bruce protocol with EKG and pulse oximetry monitoring was employed (Table 34.13). At rest, his arterial oxygen saturation was 90%. He was able to exercise for 9:56 of the standard Bruce protocol (10th–25th percentile for age and gender). His heart rate and blood pressure increased appropriately during exercise. No ectopy or STT changes developed. His oxygen saturation gradually increased during exer-

Table 34.13 Patient 34.13: physiology of an unusual right-to-left shunting. Selected data from exercise test

Stage	Heart rate (bpm)	Blood pressure (mmHg)	Oxygen saturation (%)
Rest	96	88/58	90
Stage 1	123	100/54	93
Stage 2	127	104/54	95
Stage 3	155		97
Peak	187		97
Recovery 1:00	139	112/60	94
Recovery 3:00	94		94
Recovery 5:00	92		93
Recovery 7:00	99	84/54	91

cise, reaching a maximum of 97%. It declined again during recovery.

The arterial desaturation at rest was due to the desaturated venous return from the LSVC (saturation probably ~70%) mixing in the left atrium with the (fully saturated) pulmonary venous return. The resulting mixture of saturated and desaturated blood had a saturation of 90%, entered the left ventricle, and then was pumped into the systemic arties. The unusual increase in saturations during exercise was probably due to the fact that, with treadmill exercise, the blood flow to the legs and the venous return from the legs to the inferior vena cava and right atrium increased dramatically (probably more than fivefold). The blood flow to the distribution drained by his LSVC (which is comprised primarily of the venous return from the left arm and left side of the brain), however remained relatively stable. The increased venous return to the right atrium was pumped to the lungs and then returned to the left atrium. There, it diluted out the desaturated LSVC blood to a greater extent than it did at rest. The saturation of the blood entering the left ventricle and being pumped to the systemic arteries was therefore higher than it was at rest.

This mild degree of right-to-left shunting probably had little effect upon the patient's exercise capacity. If a full cardiopulmonary exercise test had been performed, however, an elevated $\dot{V}_E/\dot{V}_{CO2}$ slope and/or low end-tidal pCO_2 may have been detected.

References

1. Rhodes J, Udelson JE, Marx GR, Schmidt CH, Konstam MA, Hijazi ZM, et al. A new noninvasive method for the estimation of peak dP/dt. Circulation. 1993;88:2693–9.
2. Rhodes J, Fulton DR, Levine JC, Marx GR. Comparison between the mean dP/dt during Isovolumetric contraction and other echocardiographic indexes of ventricular systolic function. Echocardiography. 1997;14(3):215–22.

35 Patients with Significant Lung Disease

Jonathan Rhodes

Case 35.1: Hypoplastic Left Lung

The patient was an 11-year-old boy who initially presented for evaluation on account of a history of recurrent pneumonias and a chest X-ray that revealed the heart to be shifted slightly to the left. A chest computed tomography (CT) scan revealed left pulmonary vein atresia and a hypoplastic left pulmonary artery. Increased septal markings and pleural thickening were noted throughout the left lung, consistent with chronic pulmonary edema. The left lung was somewhat hypoplastic, and there was some compensatory hypertrophy of the right lung. The central trachea and primary bronchi appear to be normal in caliber. A lung perfusion scan revealed that his left lung received only 4% of the total pulmonary blood flow. An echocardiogram revealed normal intracardiac anatomy. The left pulmonary veins were atretic and the left pulmonary artery was mildly hypoplastic. There was mild tricuspid regurgitation with a peak gradient of 20 mm Hg, indicating that pulmonary hypertension was not present. There was bidirectional flow in the left pulmonary artery. The right pulmonary artery and veins were widely patent, with a normal flow. The ventricular function was good. Clinically, the patient complained of mild exercise intolerance but was otherwise asymptomatic. His physical examination was notable only for mildly reduced breath sounds on the left. He was referred for an exercise test to further assess his cardiopulmonary status (Table 35.1).

Table 35.1 Patient 35.1: hypoplastic left lung. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	42.8
Peak$\dot{V}_{O2}$ (%predicted)	96
Peak work rate (W)	120
Peak work rate (%predicted)	98
Peak RER	1.11
Peak O_2 pulse (%predicted)	111
Peak heart rate (bpm)	169
Peak heart rate (%predicted)	88
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	55
End-tidal pCO_2 at VAT (mm Hg)	36
End-tidal pCO_2 during exercise	Low
$\dot{V}_E/\dot{V}_{CO2}$ slope	37
Forced vital capacity (%predicted)	75
FEV1 (%predicted)	73
FEF 25–75 (%predicted)	64
Breathing reserve (%)	5
Baseline arterial O_2 saturation (%)	99
Post-exercise arterial O_2 saturation (%)	98
Rhythm	Sinus rhythm throughout study
Blood pressure response	Normal

RER respiratory exchange ratio, *bpm* beats per minute, *VAT* ventilatory anaerobic threshold, *FEV1* volume exhaled in the first second of forced expiration, *FEF* forced expiratory flow

J. Rhodes (✉)
Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
e-mail: jonathan.rhodes@cardio.chboston.org

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6_35

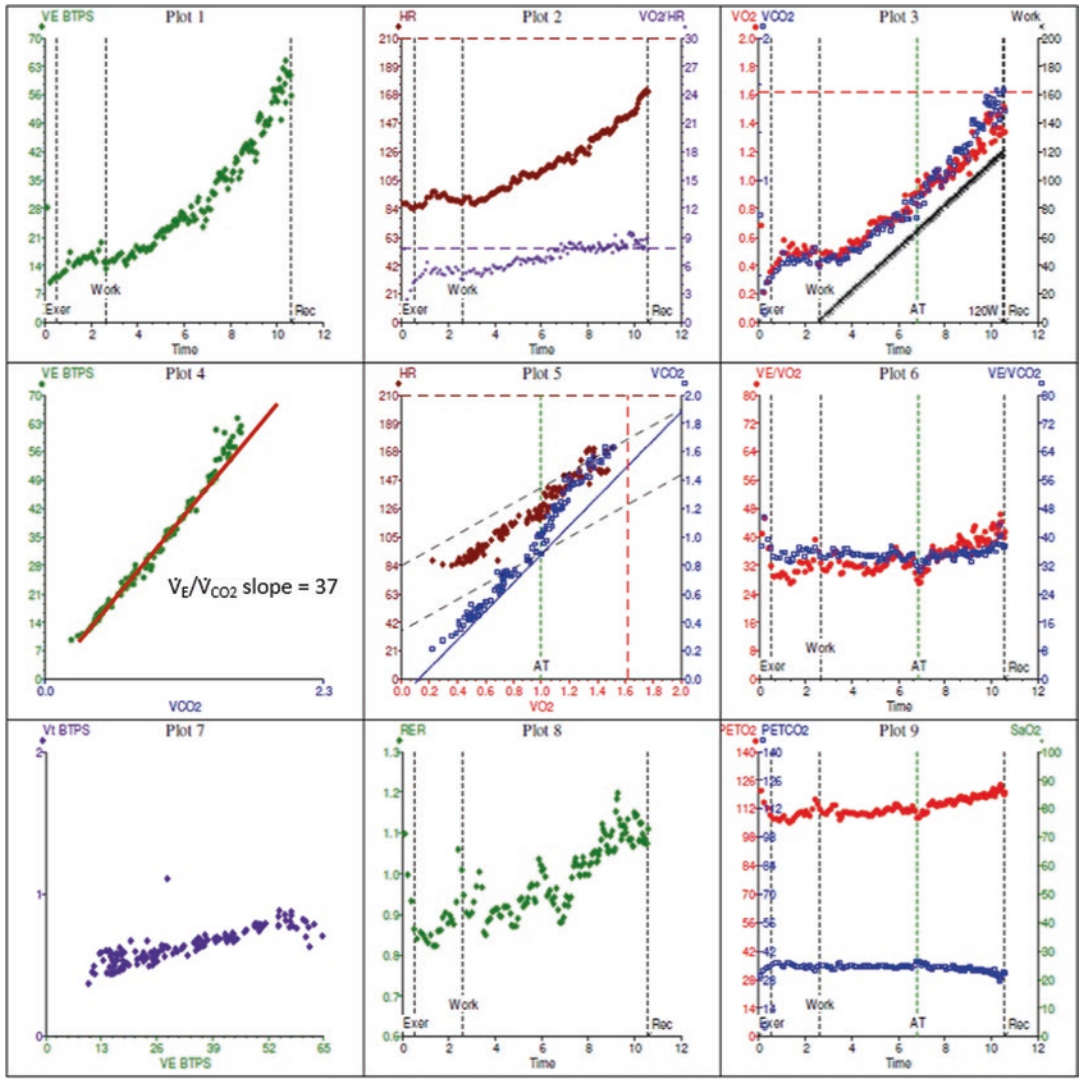


Fig. 35.1 Nine-panel graph of data from cardiopulmonary exercise test from patient 35.1: hypoplastic left lung. Abbreviations: AT ventilator anaerobic threshold, BTPS body temperature and pressure, saturated, Exer exercise; PETCO2 end-tidal pCO2, PETO2 end-tidal pO2, Rec recovery, RER respiratory exchange ratio, $\dot{V}_{CO2}$ carbon dioxide production, $\dot{V}_E$ minute ventilation, $\dot{V}_{O2}$ oxygen consumption, $\dot{V}_{O2}$/HR oxygen pulse

The CPET was performed on a cycle ergometer with a 15 W/min ramp. His peak respiratory exchange ratio was 1.11, indicating that exercise was terminated near his cardiovascular limit. His peak $\dot{V}_{O2}$, work rate, and oxygen pulse were normal, as was his $\dot{V}_{O2}$ at the ventilator anaerobic threshold. A mild restrictive-obstructive pattern was present on his baseline spirometry. No significant change was detected on post-exercise spirometry. His $\dot{V}_E/\dot{V}_{CO2}$ slope was elevated (Fig. 35.1, left middle panel), and his end-tidal pCO_2 during exercise was low (Fig. 35.1, right lower panel). His arterial oxygen saturation remained normal throughout the study. Exercise was terminated due to leg fatigue.

The patient's ability to achieve normal peak exercise parameters was probably a reflection of the fact that his right lung, and its vascular bed, had grown to compensate for the hypoplastic left lung. He was therefore able to lower his

pulmonary vascular resistance and increase his cardiac output appropriately during exercise. His left lung, however, did not participate significantly in gas exchange and was essentially "dead space." Consequently, he had to breathe more to adequately increase his alveolar ventilation, and his $\dot{V}_E/\dot{V}_{CO2}$ slope was therefore elevated. In addition, the pCO_2 of the air that was expired from his left lung was low (i.e., virtually equivalent to room air, because the left lung received virtually no blood flow and did not participate in gas exchange). When this air mixed with the air exiting the right lung, it diluted the CO_2 and lowered the end-tidal pCO_2. The low breathing reserve suggests that this patient, unlike most normal individuals and most cardiac patients, may have been limited by respiratory factors as well as, or as much as, cardiovascular factors at peak exercise.

Case 35.2: Interstitial Lung Disease

The patient was a 10-year-old boy with neuroendocrine hyperplasia of infancy (NEHI), a rare form of interstitial lung disease characterized by persistent tachypnea, hypoxia, retractions, and respiratory crackles. Radiographic studies typically reveal hyperinflation, increased interstitial markings, and ground-glass densities. When lung biopsy samples are subjected to immunostaining with antibodies to neuroendocrine cell products, increased bombesin staining is observed. The lung disease tends to improve over time [1]. This patient had all of the classical features of the condition and also had a lung biopsy that was consistent with the diagnosis. He referred for an exercise test to further assess his current cardiopulmonary status. At the time of the exercise test, he reported mild dyspnea on exertion but was otherwise asymptomatic. He was maintained only on bronchodilator therapy.

The exercise test was performed on a treadmill using the standard Bruce protocol (Table 35.2 and Fig. 35.2). Although he appeared to expend a good effort, the patient's respiratory exchange ratio at peak exercise was only 0.88. He stopped exercising due to dyspnea. His endurance time and peak $\dot{V}_{O2}$ were quite low. It was not possible to identify the ventilatory anaerobic threshold. Both the peak heart rate and peak oxygen pulse were low. His end-tidal pCO_2 rose progressively during exercise (Fig. 35.2, lower right panel). His $\dot{V}_E/\dot{V}_{CO2}$ slope, however, was normal. His baseline arterial oxygen saturation was 91%. It fell progressively during exercise, reaching a nadir of 80%. His baseline spirometry revealed a moderate-severe restrictive/obstructive pattern, which worsened significantly post-exercise. His breathing reserve at peak exercise was 37% (based upon his post-exercise spirometric measurements). Pre- and post-exercise echocardiography were also performed. No evidence of pulmonary hypertension or an intracardiac shunt was detected. The ventricular function was normal.

The low peak-exercise respiratory exchange ratio indicates that the patient did not stop

Table 35.2 Patient 35.2: interstitial lung disease. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	19.7
Peak $\dot{V}_{O2}$ (%predicted)	54
Endurance time (%ile)	<10th
Peak RER	0.88
Peak O_2 pulse (%predicted)	69
Peak heart rate (bpm)	166
Peak heart rate (%predicted)	79
Peak respiratory rate (breaths/min)	34
Peak tidal volume (%FVC)	48
Breathing reserve (%)	36.7[a]
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	Indeterminate
End-tidal pCO_2 at peak exercise (mm Hg)	49
$\dot{V}_E/\dot{V}_{CO2}$ slope	23
Pre-forced vital capacity (%predicted)	59
Pre-FEV1 (%predicted)	56
Pre-FEF 25–75 (%predicted)	48
Post-forced vital capacity (%predicted)	49
Post-FEV1 (%predicted)	43
Post-FEF 25–75 (%predicted)	21
Baseline arterial O_2 saturation (%)	91
Peak-exercise arterial O_2 saturation (%)	80
Rhythm	Sinus rhythm throughout study
Blood pressure response	Normal

[a]Based upon post-exercise spirometric measurements

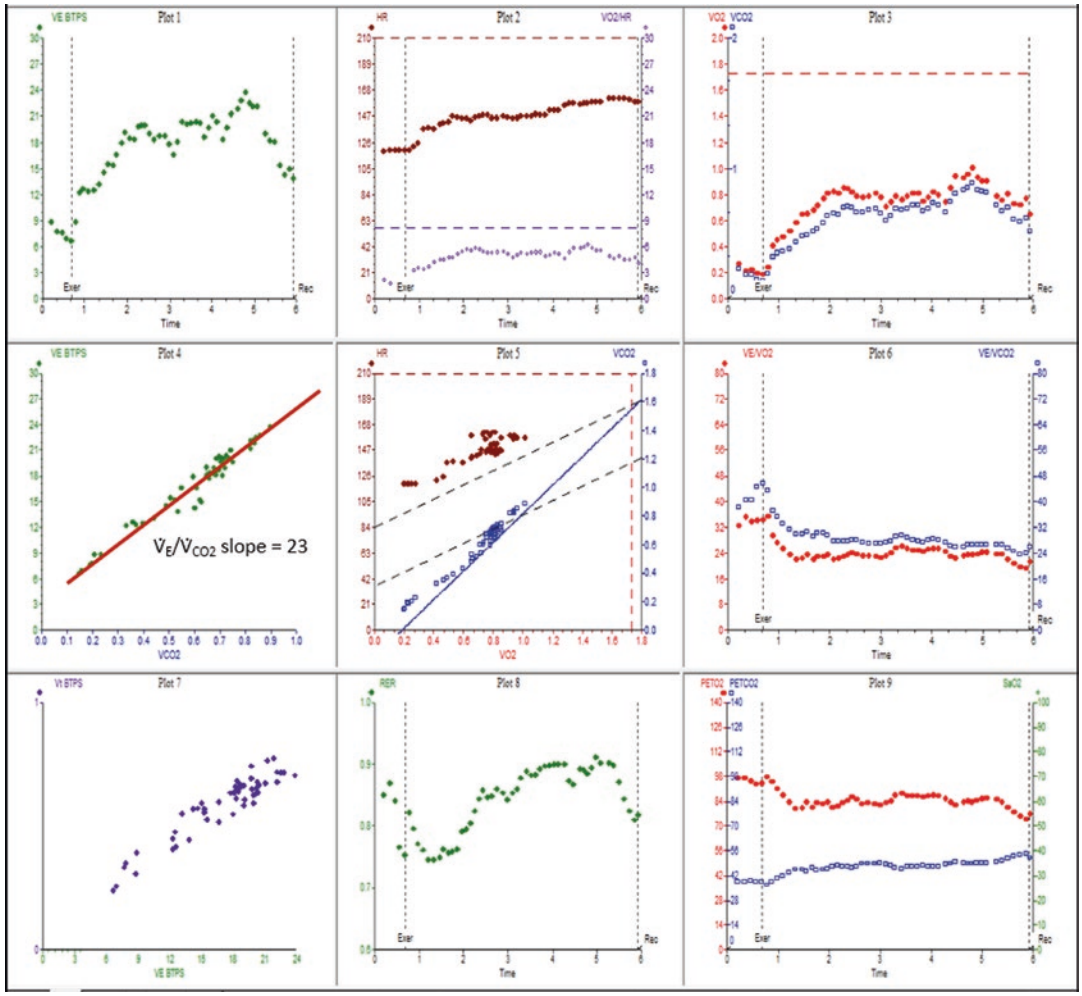


Fig. 35.2 Nine-panel graph of data from cardiopulmonary exercise test from patient 35.2: interstitial lung disease

exercising on account of a cardiovascular limitation. Rather, it is likely that pulmonary factors, which caused him to become hypoxic and retain CO_2, were responsible for the termination of exercise. Although he undoubtedly had significant airway disease (which worsened with exercise), he had an ample breathing reserve at peak exercise. This observation may indicate that impaired gas transport across the alveolar-capillary membrane, rather obstructive lung disease, was the primary factor responsible for his poor exercise performance. Moreover, isolated obstructive lung disease would not typically produce this degree of hypoxemia, unless it was associated with significant atelectasis and/or areas with extremely low ventilation/perfusion ratios. The obstructive lung disease was, however, probably responsible for "pseudonormalization" of the $\dot{V}_E/\dot{V}_{CO2}$ slope. In the presence of an isolated impairment of alveolar-capillary gas exchange, the $\dot{V}_E/\dot{V}_{CO2}$ slope would be expected to be elevated. However, the obstructive lung disease caused the patient's minute ventilation to be depressed out of proportion to his CO_2 production, because CO_2 retention raised the pCO_2 of the air he exhaled and thereby maintained his CO_2 excretion.

The patient's arterial oxygen desaturation was probably primarily due to diffusion impairment across the alveolar-capillary membrane, which resulted in pulmonary venous desaturation (i.e., there was an intrapulmonary physiologic right-to-left shunt). The desaturation worsened with exercise because the flux across the alveolar capillary membrane was limited and, as the blood flow to the alveolar capillaries increased, the blood exiting the capillaries became more and more desaturated. In addition, increased peripheral oxygen extraction caused the blood entering the capillaries during exercise to be more desaturated (compared to rest). Hence, to achieve normal post-alveolar oxygen saturations, more oxygen had to be transferred to each unit of blood. Consequently, the blood exiting the alveolar capillaries (i.e., the pulmonary venous blood) was more likely to have a low oxygen saturation.

The low oxygen pulse at peak exercise, despite the normal stress echocardiographic study, is probably explained by the fact that the patient was unable to exercise beyond (or perhaps even up to) the anaerobic threshold. Hence, the lactic acidosis that normally assists in the extraction of oxygen from hemoglobin (via the Bohr effect) at higher levels of exercise had not developed, and the saturation of the systemic venous blood returning to the right atrium was higher than normal. In addition, the patient's low arterial oxygen saturation caused the oxygen pulse to underestimate the stroke volume at peak exercise.

Case 35.3: Pulmonary Alveolar Proteinosis

The patient was a 15-year-old adolescent who was diagnosed with idiopathic pulmonary alveolar proteinosis when he was 11 years old. This diagnosis was made when he presented with a 2-year history of recurrent pneumonias and persistent, diffuse opacities on chest X-rays. Ultimately a lung biopsy was performed and revealed filling of the alveolar air spaces with granular eosinophilic material and cholesterol clefts—findings that established the diagnosis. He was managed thereafter with periodic whole lung lavage treatments, nighttime bilevel positive airway pressure (BiPAP) with supplemental oxygen, and various bronchodilator nebulizers and inhalers. He remained fairly stable on this regimen. Echocardiograms had documented normal cardiac anatomy and function and no evidence of pulmonary hypertension or intracardiac shunts. At the time of his evaluation, he had no symptoms at rest but did complain of shortness of breath with exertion. (He was nevertheless able to play baseball on his school's team!) A CPET was obtained (Table 35.3 and Fig. 35.3) to further characterize his cardiopulmonary function. A cycle ergometer with an 18 W/min ramp was employed for the study.

The patient's peak $\dot{V}_{O2}$ and peak work rate were low. However, the RER at peak exercise

Table 35.3 Patient 35.3: pulmonary alveolar proteinosis. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	24.8
Peak $\dot{V}_{O2}$ (%predicted)	61
Peak work rate (W)	101
Peak work rate (%predicted)	58
Peak RER	1.06
Peak O_2 pulse (%predicted)	76
Peak heart rate (bpm)	153
Peak heart rate (%predicted)	76
Peak respiratory rate (breaths/min)	46
Peak tidal volume (%FVC)	36
Breathing reserve (%)	47[a]
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	41
End-tidal pCO_2 at peak exercise (mm Hg)	48
$\dot{V}_E/\dot{V}_{CO2}$ slope	24
Pre-forced vital capacity (%predicted)	67
Pre-FEV1 (%predicted)	72
Pre-FEV1/FVC (%)	92
Pre-FEF 25–75 (%predicted)	73
Post-forced vital capacity (%predicted)	69
Post-FEV1 (%predicted)	64
Post-FEV1/FVC (%)	79
Post-FEF 25–75 (%predicted)	48
Baseline arterial O_2 saturation (%)	88
Peak-exercise arterial O_2 saturation (%)	78
Rhythm	Sinus rhythm throughout study
Blood pressure response	Normal

[a]Based upon post-exercise spirometric measurements

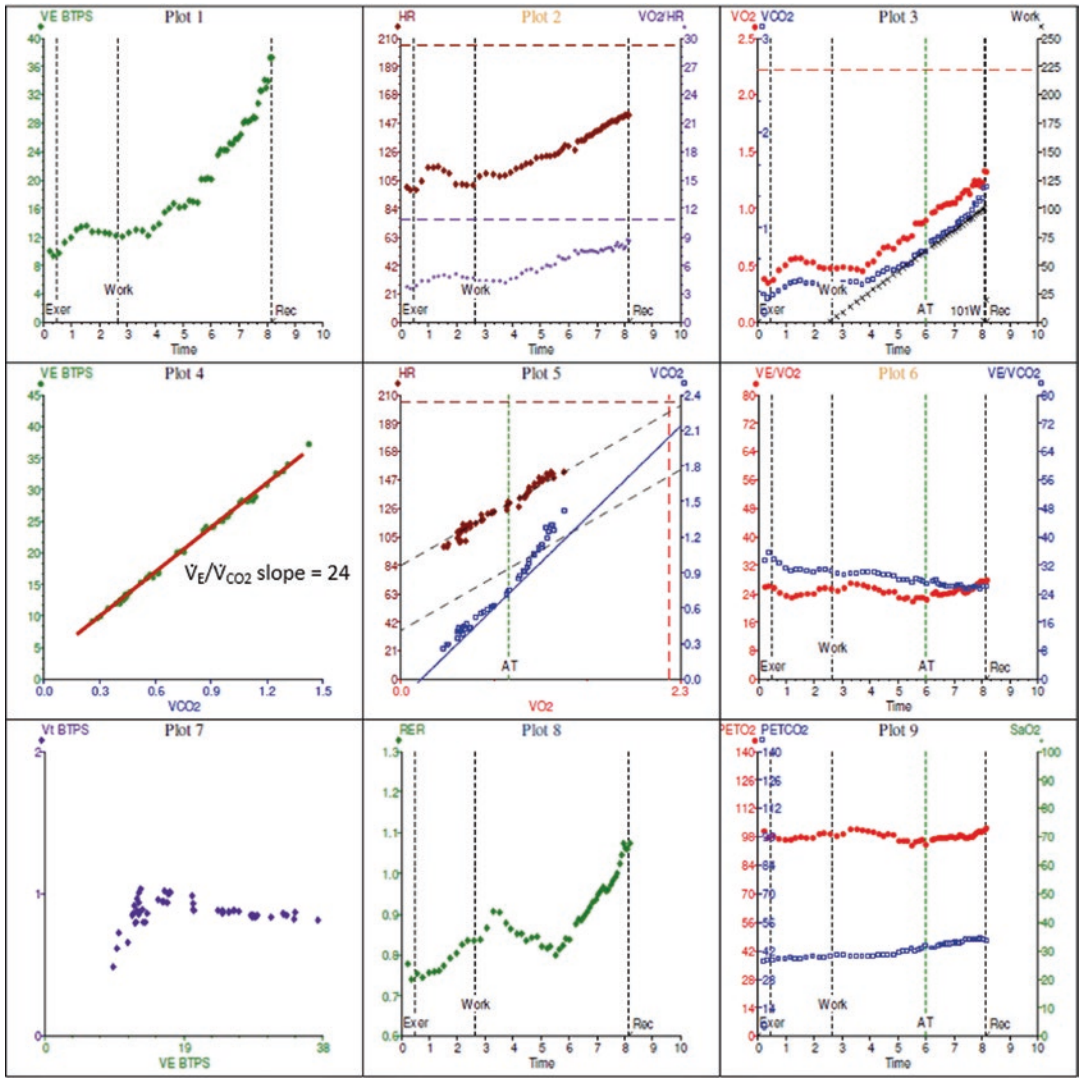


Fig. 35.3 Nine-panel graph of data from cardiopulmonary exercise test from patient 35.3: pulmonary alveolar proteinosis

was only 1.06, suggesting that exercise was not terminated on account of cardiovascular factors. The low heart rate at peak exercise supports this conjecture. Arterial desaturation was present at rest and worsened significantly during exercise. Significant CO_2 retention was present at peak exercise (Fig. 35.3, lower right panel), and the expected decline in the end-tidal pCO_2 at higher levels of exercise (which would reflect the compensatory respiratory alkalosis that should develop in response to the lactic acidosis that accumulates at exercise intensities above the anaerobic threshold) was not observed. These findings suggest that it was respiratory factors that caused the patient to stop exercising. The $\dot{V}_{O2}$ and work rate at peak exercise were low, but the $\dot{V}_{O2}$ at the anaerobic threshold was low-normal. The oxygen pulse at peak exercise was also mildly depressed. The heart rate increase during exercise was appropriate for the level of $\dot{V}_{O2}$ (Fig. 35.3, middle panel). The tidal volume at peak exercise was low and actually declined at

higher levels of exercise (Fig. 35.3, lower left panel). The $\dot{V}_E/\dot{V}_{CO2}$ slope was normal. His baseline spirometry revealed a mild restrictive/obstructive pattern. The obstructive component worsened considerably post-exercise.

The patient's arterial oxygen desaturation was probably due primarily to diffusion impairment across the alveolar-capillary membrane, which resulted in pulmonary venous desaturation (i.e., there was an intrapulmonary physiologic right-to-left shunt). The desaturation worsened with exercise because the oxygen flux across the diseased alveolar-capillary membrane was limited and, as the blood flow to the alveolar capillaries increased, the blood exiting the capillaries became more and more desaturated. In addition, increased peripheral oxygen extraction caused the blood entering the alveolar capillaries during exercise to be more desaturated (compared to rest). Hence, to achieve normal post-alveolar oxygen saturations, more oxygen had to be transferred to each unit of blood. Consequently, the blood leaving the alveolus was more likely to have a low oxygen saturation.

The patient also developed significantly more airway obstruction during exercise. This phenomenon was reflected by the more severe obstructive pattern on his post-exercise spirometry. The low tidal volume at peak exercise, and the decline in tidal volume during exercise, was probably due to air trapping secondary to the airway obstruction. The airway obstruction, as well as diffusion impairment across the alveolar-capillary membrane, probably contributed to the CO_2 retention during exercise. Ventilation/perfusion mismatch with areas of atelectasis or very low ventilation/perfusion ratios may also have contributed to the patient's hypoxemia. The unexpectedly normal $\dot{V}_E/\dot{V}_{CO2}$ slope was probably due to "pseudonormalization" due to the coexistent obstructive lung disease, rather than the absence of interstitial lung disease and/or ventilation/perfusion mismatch (the obstructive lung disease caused the patient's minute ventilation to be depressed out of proportion to his CO_2 production, because the CO_2 retention raised the pCO_2 of the air he exhaled and thereby maintained his CO_2 excretion). The fact that the patient had a substantial breathing reserve when he terminated exercise suggests that the impairment of gas exchange across the alveolar-capillary membrane, rather than the obstructive physiology, was the primary factor responsible for his exercise limitation.

Because the patient terminated exercise on account of respiratory factors, his peak exercise parameters probably did not reflect the true capabilities of his cardiovascular system. The fact that his anaerobic threshold was (low) normal and that the oxygen pulse when exercise was terminated was only mildly depressed, despite the arterial desaturation, suggest that the patient's cardiovascular function was probably fairly well preserved. Certainly, the low oxygen saturation caused the oxygen pulse to underestimate the stroke volume at peak exercise. Moreover, it is likely that the oxygen pulse would have been higher if he had exercised longer and developed a more profound lactic acidosis, which, via the Bohr effect, would have promoted the extraction of oxygen from hemoglobin.

Case 35.4: Repaired Tetralogy of Fallot with Undiagnosed Vascular Ring

The patient was an 18-year-old adolescent male who had undergone a transannular repair of tetralogy of Fallot when he was an infant. He presented for evaluation on account of dyspnea on exertion. His echocardiogram revealed mild-moderate tricuspid regurgitation with a peak gradient of 50 mm Hg, free pulmonary regurgitation, and right ventricular dilation with moderate systolic dysfunction. A CPET was obtained to further assess his current status (Table 35.4 and Fig. 35.4a). A cycle ergometer with a 25 W/min ramp was employed.

The patient stopped exercising on account of dyspnea/dry throat. His peak RER was only 1.07, suggesting that the exercise test was not terminated on account of a cardiovascular limitation. Consistent with this conjecture was the observation that his peak heart rate was also slightly low. Despite this, his peak $\dot{V}_{O2}$ and peak work rate

Table 35.4 Patient 35.4: repaired tetralogy of Fallot with undiagnosed vascular ring. Selected data from cardiopulmonary exercise tests

Parameter	Pre-Op	Post-Op
Peak $\dot{V}_{O2}$ (ml/min)	2315	2635
Peak $\dot{V}_{O2}$ (%predicted)	78	84
Peak work rate (W)	200	220
Peak work rate (%predicted)	85	94
Peak RER	1.07	1.23
Peak O_2 pulse (%predicted)	91	95
Peak heart rate (bpm)	161	155
Peak heart rate (%predicted)	86	86
Peak respiratory rate (breaths/min)	26	29
Peak minute ventilation (l/min)	54.5	77.0
Peak tidal volume (%FVC)	47	71
Breathing reserve (%)	31	28
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	42	42
End-tidal pCO_2 at peak exercise (mm Hg)	51	45
$\dot{V}_E/\dot{V}_{CO2}$ slope	20	21
Pre-forced vital capacity (%predicted)	85	79
Pre-FEV1 (%predicted)	63	72
Pre-FEV1/FVC (%)	74	93
Pre-FEF 25–75 (%predicted)	51	59
Pre-FEF max (%predicted)	37	51
Post-forced vital capacity (%predicted)	78	
Post-FEV1 (%predicted)	63	
Post-FEV1/FVC (%)	80	
Post-FEF 25–75 (%predicted)	48	
Post-FEF max (%predicted)	39	
Baseline arterial O_2 saturation (%)	99	
Peak-exercise arterial O_2 saturation (%)	99	
Rhythm	Sinus	
Blood pressure response	Normal	

were only mildly depressed and his $\dot{V}_{O2}$ at the VAT was low normal. His peak-exercise oxygen pulse was also in the normal range. His end-tidal pCO_2 rose progressively during exercise, reaching a maximum of 51 mm Hg. The expected decline in end-tidal pCO_2, reflecting the compensatory respiratory alkalosis that should develop in response to the lactic acidosis that accumulates at exercise intensities above the anaerobic threshold, was not observed (Figure 35.4a, bottom right panel). His baseline spirometry revealed an unusual pattern, with disproportionately low peak expiratory flow rates, consistent with large airway obstruction. No significant change was detected post-exercise (Fig. 35.4b). Following the CPET, a cardiac MRI was performed, which revealed severe pulmonary regurgitation (regurgitation fraction 49%), moderate tricuspid regurgitation (regurgitation fraction 35%), and a severely dilated RV (end-diastolic volume 212 ml/m^2) with only mildly depressed systolic function (ejection fraction 43%). His pulmonary blood flow distribution was normal. In addition, a vascular ring formed by a double aortic arch (unobstructed right aortic arch and a left aortic arch with an atretic segment between the left subclavian artery and a diverticulum protruding from the leftward aspect of the descending aorta) was seen, causing moderate tracheal compression.

The patient therefore had coexistent (residual) cardiovascular disease and tracheal obstruction. The tracheal obstruction impaired his ventilatory response to exercise (his $\dot{V}_E/\dot{V}_{CO2}$ slope was unusually low, probably because he could not raise his minute ventilation normally) and caused him to retain CO_2. This factor, as much or more than the residual cardiovascular disease, probably accounted for his dyspnea with exercise. Indeed, the fact that $\dot{V}_{O2}$ at the VAT and his oxygen pulse at peak exercise were normal and his peak work rate and $\dot{V}_{O2}$ were only mildly depressed—despite the fact that he did not terminate exercise on account of a cardiovascular limitation—implied that his cardiovascular function was not significantly compromised. It is likely that his unobstructed pulmonary arteries and healthy pulmonary vascular bed mitigated the hemodynamic effects of his incompetent pulmonary and tricuspid valves (see Chap. 14).

Following this CPET, he underwent surgery to release the vascular ring and replace the pulmonary valve. A subsequent CPET study revealed improvement in his exercise function and CO_2 retention during exercise (Table 35.4 and Fig. 35.4c). The expected decline in end-tidal pCO_2 at higher levels of exercise was now present (Fig. 35.4c, bottom right panel). Significantly, he was now able to achieve a peak RER of 1.23, suggesting that exercise was terminated on

a

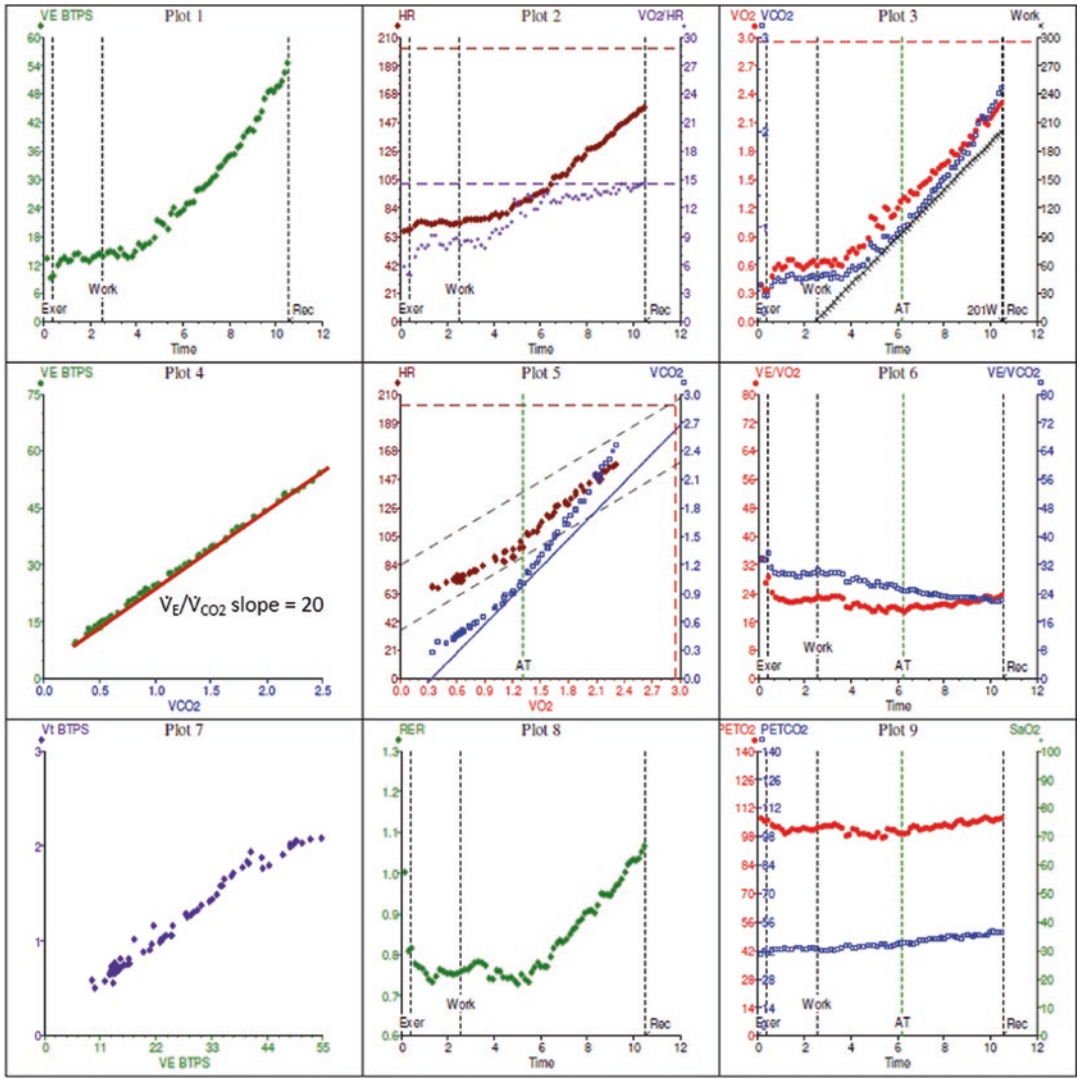
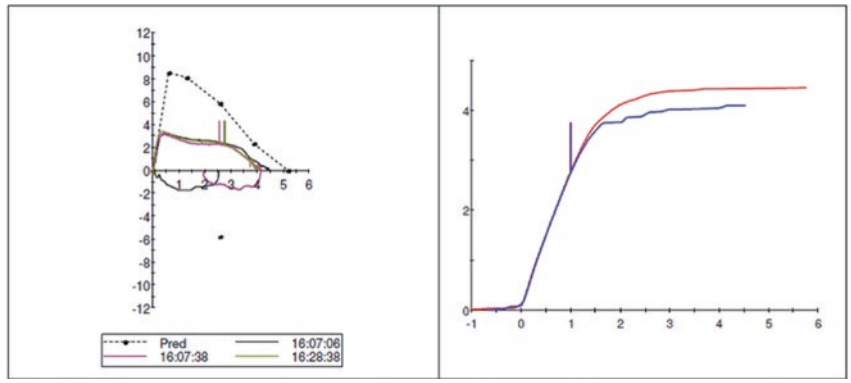


Fig. 35.4 (**a**) Nine-panel graph of data from cardiopulmonary exercise test from patient 35.4: Repaired tetralogy of Fallot with undiagnosed vascular ring. (**b**) Preoperative post-exercise spirometric measurements. (**c**) Nine-panel graph of data from cardiopulmonary exercise test following surgery to release the vascular ring and replace the pulmonary valve. (**d**) Postoperative spirometric measurements. Note that the expiratory flow values at high lung volumes are significantly reduced. This pattern is consistent with large airway (e.g., tracheal) obstruction

b

	Pre-Exercise			Post-Exercise		
	Actual	Pred	%Pred	Actual	%Pred	%Chng
---- SPIROMETRY ----						
FVC (L)	4.45	5.20	85	4.09	78	-8
FEV1 (L)	2.79	4.40	63	2.77	63	+0
FEV1/FVC (%)	63	85	74	68	80	+7
FEF 25% (L/sec)	2.85	8.11	35	2.75	33	-3
FEF 75% (L/sec)	1.94	2.30	84	1.56	67	-19
FEF 25-75% (L/sec)	2.47	4.79	51	2.34	48	-5
FEF Max (L/sec)	3.17	8.53	37	3.37	39	+6



c

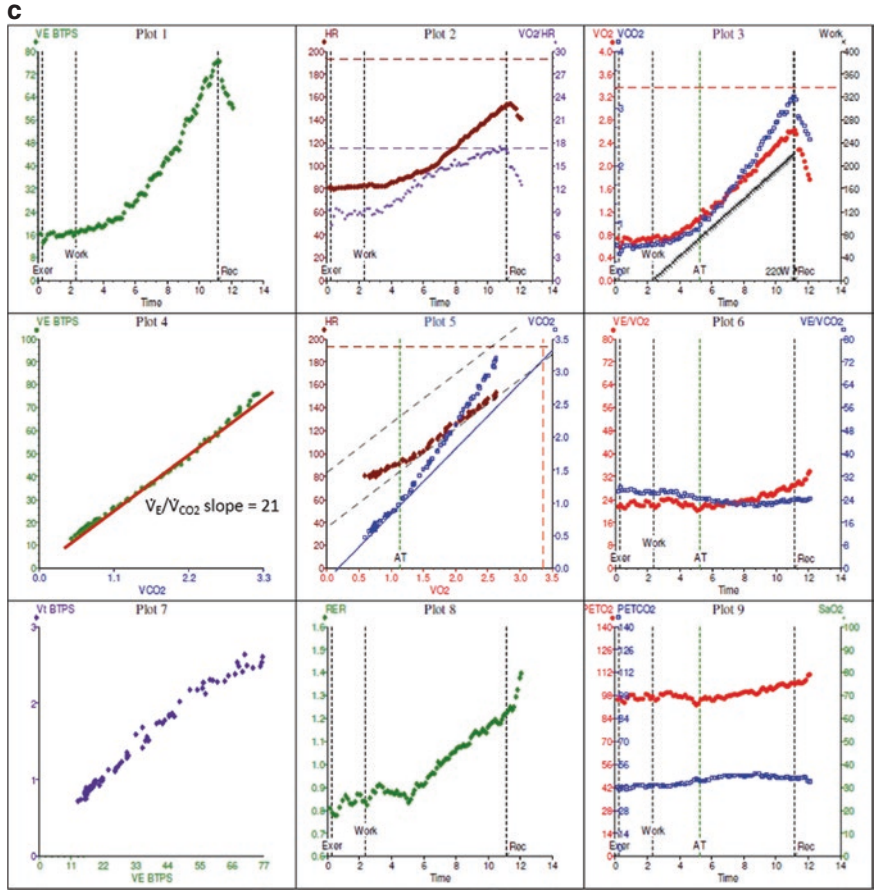


Fig. 35.4 (continued)

d

	Actual	Pred	%Pred
---- SPIROMETRY ----			
FVC (L)	3.72	4.68	79
FEV1 (L)	2.85	3.94	72
FEV1/FVC (%)	77	82	93
FEF 25% (L/sec)	3.97	8.50	46
FEF 75% (L/sec)	1.20	2.23	53
FEF 25-75% (L/sec)	2.54	4.29	59
FEF Max (L/sec)	4.54	8.85	51
FIVC (L)	3.19		
FIF Max (L/sec)	2.45		

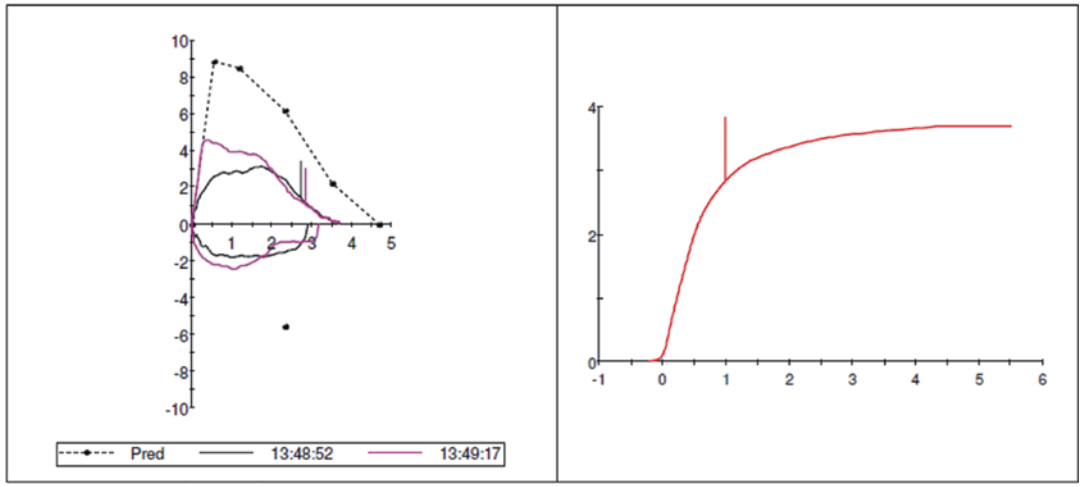


Fig. 35.4 (continued)

account of a cardiovascular, rather than a respiratory limitation. In addition, his minute ventilation at peak exercise was significantly higher than it had been preoperatively. Although his spirometric measurements remained abnormal (Fig. 35.4d), they were significantly improved compared to preoperative measurements, with a 38% increase in peak expiratory flow rate.

Case 35.5: "Repaired" Pulmonary Artery Sling/Obstructive Lung Disease

The patient was a 14-year-old adolescent who had undergone repair of a left pulmonary artery sling and tracheal stenosis when he was a neonate. He also had a hypoplastic right lung. Postoperatively, he was followed with a degree of residual airway obstruction, mild scoliosis, and mild pulmonary hypertension that gradually improved over time. At the time of his evaluation, he denied significant cardiopulmonary symptoms. He felt that his exercise capacity was good, albeit not quite as good as his peers. His echocardiogram revealed mild residual left pulmonary artery stenosis. His ventricular function was normal and there was no evidence of pulmonary hypertension. A lung perfusion scan revealed that his left lung received 76% and right lung 24% of the total pulmonary blood flow. An exercise test (Table 35.5 and Fig. 35.5) was performed to further assess his current cardiopulmonary status.

A cycle ergometer with a 20 W/min ramp was used for the study. The respiratory exchange ratio at peak exercise was 1.13, indicating that a good effort was expended. He stopped exercising due to shortness of breath. His peak $\dot{V}_{O2}$, peak oxygen pulse, and $\dot{V}_{O2}$ at the ventilatory anaerobic threshold were somewhat depressed. His peak heart rate was normal, but his heart rate increase relative to his $\dot{V}_{O2}$ was somewhat excessive (Fig. 35.5, middle panel). His $\dot{V}_E/\dot{V}_{CO2}$ was normal. His end-tidal pCO_2 tended to be high, and the expected decline in end-tidal pCO_2 at higher levels of exercise (to compensate for the lactic acidosis that accumulates above the anaerobic threshold) was not observed. Moreover, his tidal volume at peak exercise was slightly low, and his breathing reserve was quite low. His pre-exercise spriometry revealed a severe obstructive pattern; there was a modest improvement post-exercise. His arterial oxygen saturation remained normal (99%) throughout the study.

Table 35.5 Patient 35.5: "repaired" pulmonary artery sling/obstructive lung disease. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	35.6
Peak $_{O2}$ (%predicted)	72
Peak work rate (W)	158
Peak work rate (%predicted)	72
Peak RER	1.13
Peak O_2 pulse (%predicted)	73
Peak heart rate (bpm)	187
Peak heart rate (%predicted)	98
Peak respiratory rate (breaths/min)	42
Peak tidal volume (%FVC)	42
Breathing reserve (%)	−19
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	31
End-tidal pCO_2 at peak exercise (mm Hg)	47
$\dot{V}_E/\dot{V}_{CO2}$ slope	23
Pre-forced vital capacity (%predicted)	76
Pre-FEV1 (%predicted)	32
Pre-FEV1/FVC (%)	36
Pre-FEF 25–75 (%predicted)	11
Post-forced vital capacity (%predicted)	79
Post-FEV1 (%predicted)	34
Post-FEV1/FVC (%)	37
Post-FEF 25–75 (%predicted)	15
Baseline arterial O_2 saturation (%)	99
Peak-exercise arterial O_2 saturation (%)	99
Rhythm	Sinus
Blood pressure response	Normal

The low breathing reserve and elevated end-tidal pCO_2 at peak exercise indicated that the patient's exercise function was probably limited by respiratory as well as cardiovascular factors. The severe obstructive pattern on baseline and post-exercise spirometry, as well as the low tidal volume at peak exercise, were consistent with obstructive lung disease with probable air trapping. The low peak work rate, peak $\dot{V}_{O2}$, peak stroke volume (as reflected by the peak oxygen pulse), and ventilatory anaerobic threshold were also consistent with residual cardiovascular disease. The excessive heart rate increase was likely a compensatory autonomic response to the low stroke volume during exercise. Based upon the patient's clinical history, it is tempting to speculate that his pulmonary vascular bed remained abnormal, and that although his resting pulmonary artery pressures were normal, his pulmonary vascular resistance did not fall appropriately with exercise. Exercise-induced pulmonary hypertension may have therefore been present and could have accounted for the patient's poor aerobic function. A stress echocardiogram would have been helpful in this regard, but, unfortunately, this study was not obtained.

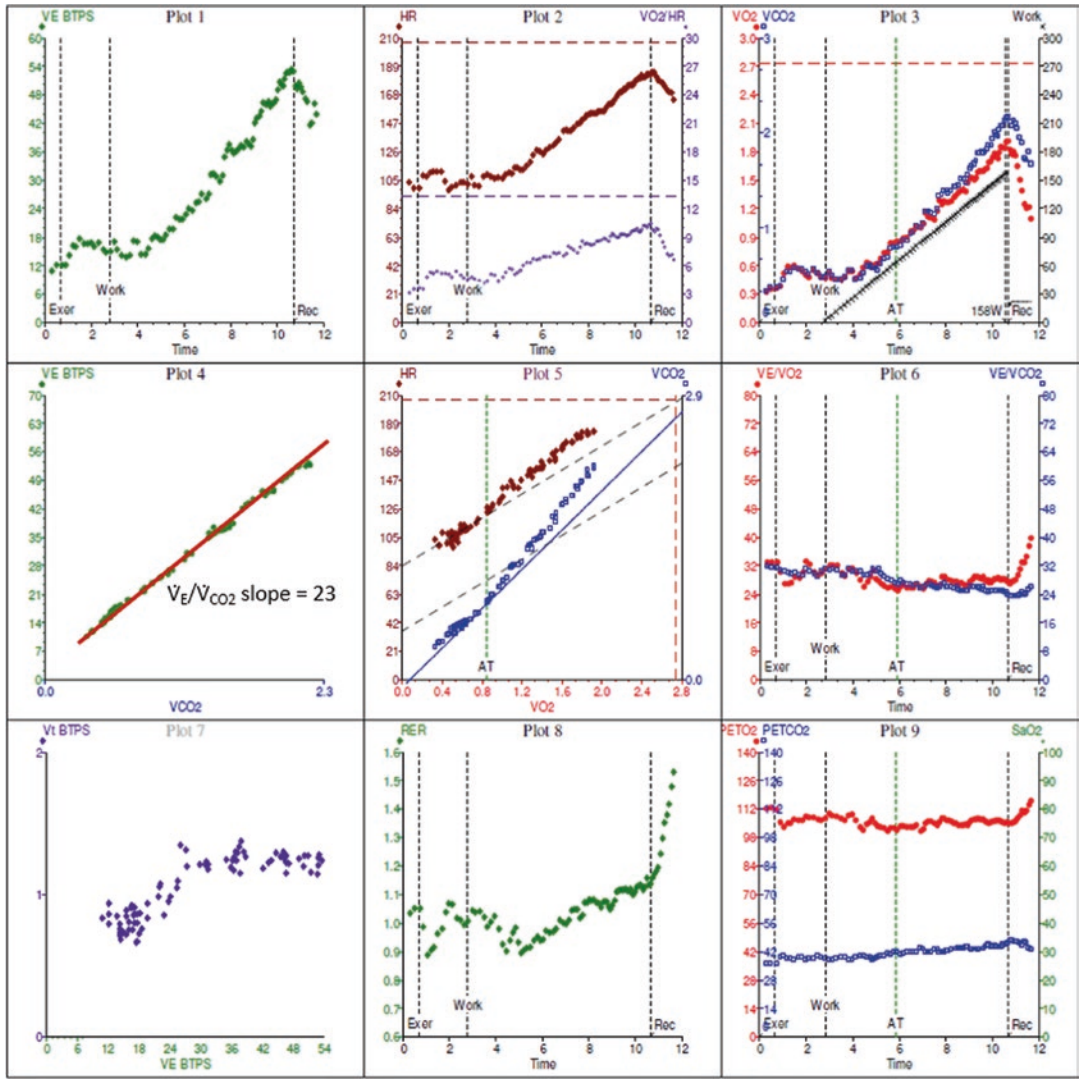


Fig. 35.5 Nine-panel graph of data from cardiopulmonary exercise test from patient 35.5: "repaired" pulmonary artery sling/obstructive lung disease

Case 35.6: Bronchiolitis Obliterans

The patient was a 10-year-old boy who developed bronchiolitis obliterans, following an episode of mycoplasma pneumonia complicated by Stevens–Johnson Syndrome when he was 4 years old. The condition was diagnosed on the basis of his clinical picture (chronic respiratory distress and dyspnea on exertion, bilateral crackles on auscultation of his chest), chest X-ray evidence of hyperinflation, and a high-resolution chest CT scan that revealed radiologic findings (diffuse bronchial wall thickening, bronchiectasis, ill-defined areas of ground-glass opacity throughout the lung parenchyma) that were classic for this condition. Previous pulmonary function tests had revealed a severe obstructive pattern, which improved slightly over the years but remained quite abnormal. Echocardiograms had never detected evidence of pulmonary hypertension or intracardiac shunts.

Table 35.6 Patient 35.6: bronchiolitis obliterans. Selected data from cardiopulmonary exercise test

Parameter	Value
Peak $\dot{V}_{O2}$ (ml/kg/min)	35.1
Peak $\dot{V}_{O2}$ (%predicted)	82
Endurance time (%ile)	25–50th
Peak RER	1.03
Peak O_2 pulse (%predicted)	86
Peak heart rate (bpm)	200
Peak heart rate (%predicted)	95
Peak respiratory rate (breaths/min)	31
Peak tidal volume (%FVC)	35
Breathing reserve (%)	19
$\dot{V}_{O2}$ at VAT (% of predicted peak $\dot{V}_{O2}$)	59
End-tidal pCO_2 at peak exercise (mm Hg)	47
$\dot{V}_E/\dot{V}_{CO2}$ slope	23
Pre-forced vital capacity (%predicted)	79
Pre-FEV1 (%predicted)	39
Pre-FEV1/FVC (%)	44
Pre-FEF 25–75 (%predicted)	15
Post-forced vital capacity (%predicted)	73
Post-FEV1 (%predicted)	39
Post-FEV1/FVC (%)	47
Post-FEF 25–75 (%predicted)	15
Baseline arterial O_2 saturation (%)	96
Peak-exercise arterial O_2 saturation (%)	88
Rhythm	Sinus
Blood pressure response	Normal

The exercise test was obtained to further assess his current cardiopulmonary status (Table 35.6 and Fig. 35.6). At the time of the exercise test, the patient claimed to have normal exercise capacity and to be asymptomatic.

The exercise test was performed on a treadmill, using the standard Bruce protocol. His pre-exercise spirometry revealed a severe obstructive pattern. His respiratory exchange ratio at peak exercise was low. His peak heart rate, however, was normal. His endurance time and peak-exercise oxygen pulse were in the normal range, and his peak $\dot{V}_{O2}$ was only mildly depressed. His anaerobic threshold was normal. His breathing reserve and tidal volume at peak exercise were low. His end-tidal pCO_2 was elevated, especially at higher levels of exercise. He also developed mild arterial oxygen desaturation at higher levels of exercise. His $\dot{V}_E/\dot{V}_{CO2}$ was normal. Post-exercise spirometry was similar to the baseline study.

The low peak-exercise respiratory exchange ratio suggests that exercise was not terminated on account of a cardiovascular limitation. The low breathing reserve and the CO_2 retention at peak exercise, however, are consistent with a respiratory limitation. This conclusion is supported by the patient's clinical history and the spirometric measurements, as well as the low tidal volume at peak exercise (consistent with air trapping). Indeed, the patient's cardiovascular response to exercise appeared to be remarkably well preserved. The arterial desaturation during exercise probably resulted from perfusion of alveoli that received little or no aeration secondary to the severe small airway disease. The saturation of the blood leaving these alveoli would be low, and the consequent pulmonary venous desaturation would result in systemic arterial desaturation. The normal $\dot{V}_E/\dot{V}_{CO2}$ was probably the result of "pseudonormalization," i.e., ventilation/perfusion mismatch coexisting with significant obstructive lung disease.

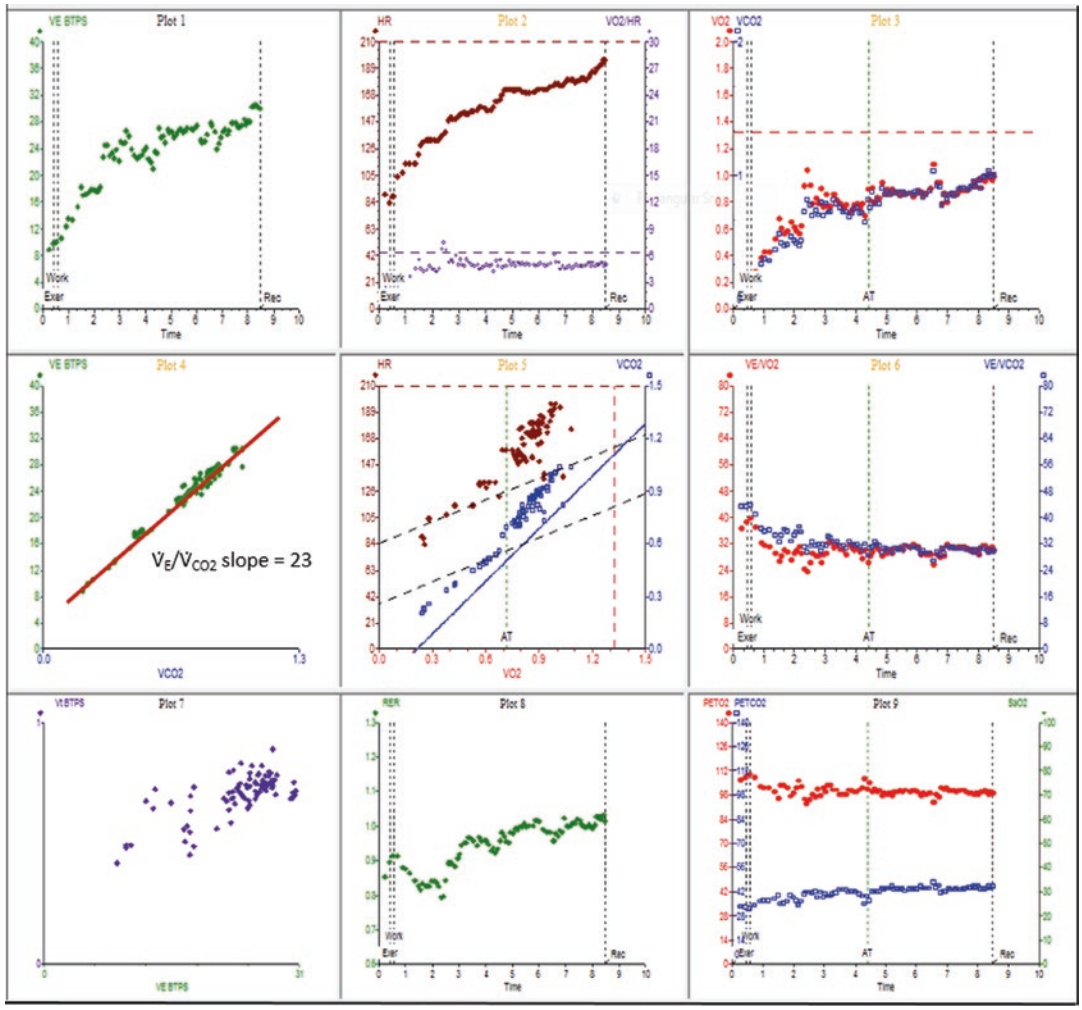


Fig. 35.6 Nine-panel graph of data from cardiopulmonary exercise test from patient 35.6: bronchiolitis obliterans

Reference

1. Deterding RR, Pye C, Fan LL, Langston C. Persistent tachypnea of infancy is associated with neuroendocrine cell hyperplasia. Pediatr Pulmonol. 2005;40(2):157–65.

Appendix

Prediction Equations and Other Useful Equations

Peak Oxygen Consumption (Peak $\dot{V}_{O2}$)

For boys <18 yrs: Peak $\dot{V}_{O2}$ (ml/min) = 43.6 × Ht (cm) − 4547 [1]
For girls <18 yrs: Peak $\dot{V}_{O2}$ (ml/min) = 22.5 × Ht (cm) − 1838 [1]

(*These are the most commonly used equations for pediatric patients. They are for cycle ergometry; add 7.5% for treadmill studies. These equations are inappropriate for children <130 cm tall*)

For boys <18 yrs: Peak $\dot{V}_{O2}$ (ml/min) = 52.8 × Wt (kg) − 303 [2]
For girls <18 yrs: Peak $\dot{V}_{O2}$ (ml/min) = 28.5 × Wt (kg) + 288 [2]

(*These equations are most appropriate for tall, thin children* (*BMI < 19.0*). *They are for cycle ergometry; add 8% for treadmill studies*)

For boys <130 cm: Peak $\dot{V}_{O2}$ (ml/min) = 42 × (ideal bodyweight-for-height; kg) [1]
For boys <130 cm: Peak $\dot{V}_{O2}$ (ml/min) = 38 × (ideal bodyweight-for-height; kg) [1]

(*These equations are most appropriate for children <130 cm tall. They are for cycle ergometry; add 8% for treadmill studies*)

For adult males: Peak $\dot{V}_{O2}$ (ml/min) = 34.5 × Ht (cm) − 28 × age (yrs) + 22 × Wt (kg) − 3760 [3]
For adult females: Peak $\dot{V}_{O2}$ (ml/min) = 24.9 × Ht (cm) − 18 × age (yrs) + 10 × Wt (kg) − 2260 [3]

(*These equations are most appropriate for adults. They are for cycle ergometry; add 8% for treadmill studies*)

For normal or overweight adult males:

Peak $\dot{V}_{O2}$ (L/min) = 0.0337 × Ht (cm) − 0.000165 × Age × Ht (cm) − 1.963 + 0.006 [Wt (kg) − (0.79 × Ht (cm)) − 60.7] [4]

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6

For underweight adult males:

Peak $\dot{V}_{O2}$ (L/min) = 0.0337 × Ht (cm) − 0.000165 × Age × Ht (cm) − 1.963 + 0.014 [Wt (kg) − (0.79 × Ht (cm)) − 60.7] [4]

For adult females:

Peak $\dot{V}_{O2}$ (L/min) = (0.001 × Ht × (14.783–0.11 × Age) + 0.006 [Wt − 0.65 × Ht − 42.8] [4]

(*The above 3 alternative equations are for cycle; multiply by 1.11 for treadmill studies. Use age of 30 yrs for adults younger than 30 yrs*)

Peak Heart Rate

Peak Heart Rate = 220 − Age (yrs); multiply by 0.925 for cycle, rather than treadmill, exercise.

Peak Oxygen Pulse

Peak Oxygen Pulse (ml/beat) = (Predicted Peak $\dot{V}_{O2}$ (ml/min))/(Predicted Peak Heart Rate (bpm))

Peak Work Rate (Pk WR)

Pk WR (Watts) = 2.64 × Ht (cm) − 1.55 × Age (yrs) + 0.91 × Wt (kg) − 40.6S – 256; S = 0 for males; S = 1 for females [5]

Heart Rate Reserve (HRR)

HRR (bpm) = Peak HR (bpm) − Resting HR (bpm)

Chronotropic Index

Chronotropic Index = 100 × (HRR)/(Predicted Peak HR − Resting HR)

Maximum Voluntary Ventilation (MVV)

MVV = FEV1 × 40

Breathing Reserve

Breathing Reserve = 100 × (MVV − Peak $\dot{V}_E$)/MVV

$\dot{V}_{O2}$ at the Anaerobic Threshold (VAT)[1]

For boys <18 yrs: VAT (ml/min) = 22.6 × Ht (cm) − 2220 [1]
For girls <18 yrs: VAT (ml/min) = 12.5 × Ht (cm) − 968 [1]

References

1. Cooper DM, Weiler-Ravell D. Gas exchange response to exercise in children. Am Rev Respir Dis. 1984;129(2,Pt 2):S47–S8.
2. Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. Aerobic parameters of exercise as a function of body size during growth in children. J Appl Physiol. 1984;56:628–34.
3. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. Am Rev Respir Dis. 1985;131(5):700–8.
4. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun XG, et al. Principles of exercise testing and interpretation. 5th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012.
5. Jones NL. Clinical exercise testing. 4th ed. Philadelphia: W.B. Saunders; 1997. p. 243.

[1] *For all subjects, the VAT should normally exceed 40% of the predicted peak* $\dot{V}_{O2}$.

Index

J. Rhodes et al. (eds.), *Exercise Physiology for the Pediatric and Congenital Cardiologist*,
https://doi.org/10.1007/978-3-030-16818-6