Exercise Physiology for the Pediatric and Congenital Cardiologist

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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.

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Part I

The Normal Cardiopulmonary Response to Exercise

Biochemistry of Exercise

1

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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:

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

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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

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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

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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.

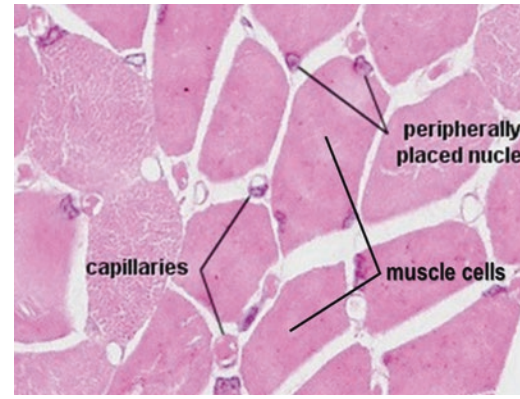

Fig. 2.1 Skeletal muscle

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].

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- 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.

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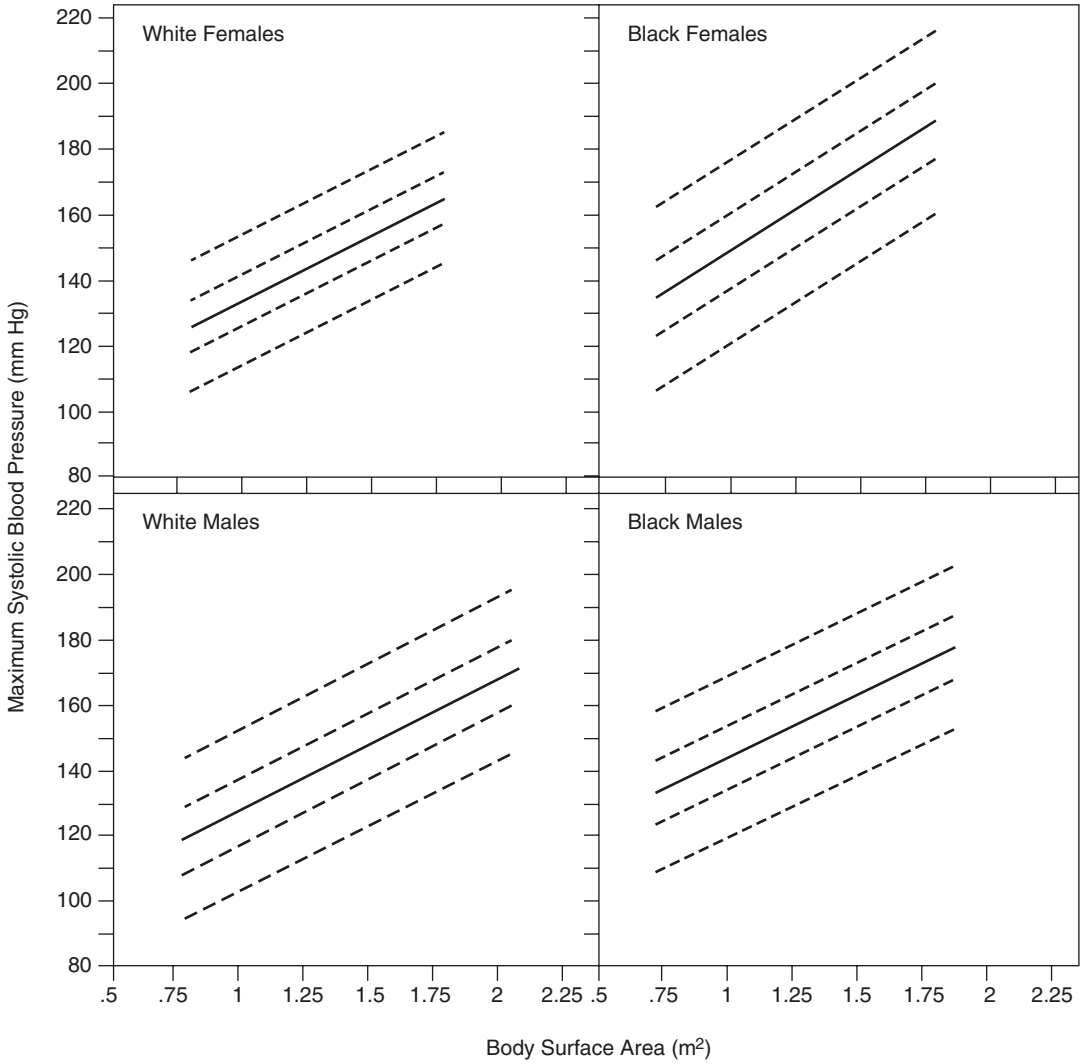

Fig. 3.1 Nomograms of maximum systolic blood pressure (mm Hg) against body surface area. The solid line is the regression line; the dashed lines represent the 5th, 25th, 75th, and 95th percentile prediction limits. (Reprinted with permission from [1])

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,

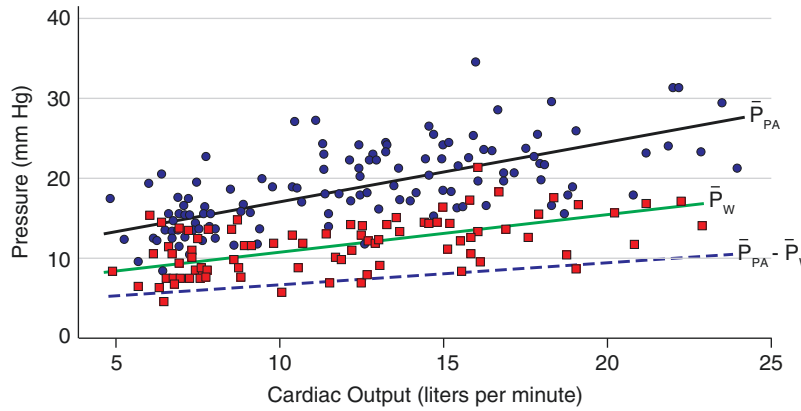

Fig. 3.2 Changes in cardiac output, mean pulmonary artery pressure (P_{PA}, black line), pulmonary capillary wedge pressure (P_W, green line), and transpulmonary gradient (P_{PA}-P_W, dotted blue line) during exercise. Note that the fivefold increase in cardiac output is associated with only a modest 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