Exercise Testing for Primary Care and Sports Medicine Physicians

Corey H. Evans MD, MPH · Russell D. White MD
Editors

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Springer

Editors
Corey H. Evans MD, MPH
Director of Medical Education
St. Anthony's Hospital
Private Practice Family Physician
Florida Institute of Family Medicine
St. Petersburg, FL, USA
email@coreyevansmd.com

Russell D. White MD
Professor of Medicine
Director, Sports Medicine Fellowship
Department of Community and Family Medicine
University of Missouri—Kansas City
Truman Medical Center Lakewood
Kansas City, MO, USA
jockdoc2000@hotmail.com

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This book is dedicated to Myrvin H. Ellestad, MD, and Victor F. Froelicher, MD. Their work and textbooks in the field of exercise and exercise testing are truly the bibles in this field and have helped countless physicians. We appreciate their guidance, friendship, and support over the years and their encouragement of exercise testing among primary care physicians.

Foreword

This book by Corey H. Evans, Russell D. White, and coauthors is a gem. There was a time when exercise testing was largely limited to cardiologists, but no more. Exercise testing, which provides information on fitness, the risk of coronary disease, and all around vitality, is now being performed in the offices of primary care physicians across the United States.

Although there is a significant risk in some populations, a careful doctor who takes the trouble to become knowledgeable in exercise physiology and the pathophysiology of coronary artery disease can use exercise testing to improve his ability to give excellent, preventive medicine.

Over the years I have read many books on this subject, and even contributed to some, and this one rates right up there with the best. Like many multiauthored books there is some repetition, but this is not all bad. A careful study of the various chapters will provide a depth of knowledge that will come in good stead when problems arise.

I can especially recommend the chapter on exercise physiology. When the reader has mastered the material presented in this chapter, he has acquired a knowledge base so that he can become an expert in exercise testing equal to almost anyone.

Over the years I have been privileged to know several of the authors and have followed their publications. Their contributions to our knowledge base in this field have been considerable. Acquiring this book and becoming familiar with its contents will set you apart in the field of exercise testing.

Myrvin H. Ellestad
Long Beach, CA
July 2008

Preface

With more than 40 years of experience between us teaching exercise testing on the national level, it is a pleasure for us to present a book on exercise testing for primary physicians. As primary care physicians, we both share strong interests in sports medicine, exercise promotion and testing, and prevention of cardiovascular disease. It is our desire to develop a text that primary care physicians can use to assess fitness, encourage and prescribe exercise, and discuss tools to evaluate our patients and athletes. We also wanted to share the basic and advanced concepts behind exercise testing so that readers can master the principles and use the exercise test in their practices. We strongly believe that the exercise test is invaluable for many of these purposes and should be widely used by primary care physicians.

Over the years we have been fortunate to teach and write with many of the national leaders in the field of exercise and exercise testing including Drs. Myrvin Ellestad, Victor Froelicher, and Nora Goldschlager. We have included these nationally recognized leaders as coauthors in this text and we appreciate their support.

It is our desire to help the reader know when statements are evidence based and the strength of the evidence. To that end, we have used a common rating system, used by the American College of Cardiology and others. When possible statements and recommendations will be categorized into three classes, based on the evidence and consensus of experts:

- Class I: There is evidence and/or general agreement that a given procedure, treatment, or recommendation is useful and effective.
- Class II: There is conflicting evidence and/or a divergence of opinions about the usefulness/efficacy of a treatment, procedure, or recommendation
    - Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy
    - Class IIb: Usefulness/efficacy is less well established.
- Class III: Conditions for which there is evidence and/or general agreement that the treatment/procedure is not useful/effective or actually harmful.

In addition, where applicable we use the following levels of evidence:

- Level of evidence A: Data were derived from multiple randomized clinical trials that involved large numbers of patients.

- Level of evidence B: Data were derived from a limited number of randomized trials that involved small numbers of patients or from careful analysis of nonrandomized studies or observational registries.
- Level of evidence C: Expert consensus was the primary basis for the recommendation.

The book is divided into initial chapters on the physiology of exercise and the performance of the exercise test. This includes the equipment, protocols, and interpretation. The next section discusses common abnormal examples, exercise testing coupled with imaging techniques, and the important area of risk stratification. This includes using the exercise test and other tests to stratify patients with chest pain, asymptomatic patients, preoperative patients, and those after angioplasty and coronary artery bypass graft (CABG) surgery.

Because health promotion is essential to improving our patients' lives, we included a chapter on using the exercise test and other tools in our practices to create lifestyle changes. The medical–legal aspects of exercise testing are also discussed.

The final section deals with fitness and sports medicine topics. It is important for primary physicians to understand how to evaluate and promote fitness. Since gas analysis is the best way to directly measure fitness, we felt it was important to introduce readers to gas analysis as an additional component of the exercise test. The last two chapters deal with testing both asymptomatic and symptomatic athletes. Finally, we have included a chapter using case studies to illustrate many of the important and interesting points. We certainly want to thank all of the authors for their contributions toward making this book a reality, for without their efforts we could never have finished this project. Also, many thanks to the help and patience of our editor, Margaret Burns.

We sincerely hope the readers find this text helpful in the day-to-day management of patients as we all strive to improve the lives of our patients. As we battle against obesity, diabetes, and heart disease in the US, we hope this reference enables the primary care physicians to promote fitness and exercise as well as to use tools herein to evaluate the diseases associated with obesity and inactivity.

On a personal note we would like to acknowledge our families for their support. I (RDW) would like to thank my wife, Dara, for her constant encouragement. And I (CHE) would like to thank my father, Paul Evans, for his loving support and lifelong commitment to a personal exercise program. Dad, you certainly set a great example, and now in your eighties, you are still reaping the benefits. May my boys and I continue this great tradition.

St. Petersburg, FL, USA — Corey H. Evans
Kansas City, MO, USA — Russell D. White
July 2008

Contents

Part IV Case Studies

Contributors

Michael Altman Department of Family Medicine, University of Texas Health Science Center, Houston, TX, USA, Michael.A.Altman@uth.tmc.edu

Patricia A. Deuster Department of Military and Emergency Medicine, Uniformed Services University, Consortium for Health and Military Performance, Bethesda, MD, USA, pdeuster@usuhs.mil

Kevin Edward Elder HealthPoint Medical Group; Department of Family Medicine, University of South Florida, Tampa, FL, USA, kelder@tampabay.rr.com

Myrvin H. Ellestad Exercise Laboratory, Memorial Heart Institute; Department of Cardiology, University of California, Irvine School of Medicine, Long Beach, CA, USA, mellestad@memorialcare.org

Corey H. Evans St. Anthony's Hospital, St. Petersburg, FL; Florida Institute of Family Medicine, St. Petersburg, FL, USA, email@coreyevansmd.com

Karl B. Fields Moses Cone Health System, Greensboro, NC; Department of Family Medicine, University of North Carolina at Chapel Hill, Greensboro, NC, USA, bert.fields@mosescone.com

Grant Fowler Department of Family and Community Medicine, The University of Texas Health Science Center Houston, Houston, TX, USA, grant.c.fowler@uth.tmc.edu

Victor F. Froelicher Department of Cardiology, Stanford/Palo Alto Veterans Affairs Health Care Center, Palo Alto, CA, USA, vcimd@pabell.net

Nora Goldschlager Department of Medicine, Division of Cardiology, University of California San Francisco, San Francisco, CA, USA NGoldschlager@medsfgh.ucsf.edu

George D. Harris Department of Community and Family Medicine, University of Missouri-Kansas City, School of Medicine, Truman Medical Center—Lakewood, Kansas City, MO, USA, george.harris@tmcmed.org

David L. Herbert David L. Herbert and Associates, LLC, Canton, OH, USA, herblegal@aol.com

William G. Herbert Laboratory for Health & Exercise Science, Department of Human Nutrition, Foods, & Exercise, Virginia Tech, Blacksburg, Virginia; The Exercise Standards and Malpractice Reporter, Canton, OH, USA

Bryan C. Hughes Oak Grove Medical Clinic, Oak Grove, MO, USA, Big1500@hotmail.com

Joseph S. Janicki Department of Cell Biology and Anatomy, University of South Carolina School of Medicine, Columbia, SC, USA, jjanicki@gw.med.sc.edu

Ajoy Kumar Family Practice Training Program, Bayfront Medical Center, St. Petersburg, FL, USA, vsingh@health.usf.edu

Matthew T. Kunar 4th BCT, 82nd Airborne Division, Fort Bragg, NC, USA, kunar36@msn.com

Steven C. Masley University of South Florida, Tampa; Masley Optimal Health Center, St. Petersburg, FL, USA, steven@drmasley.com

Patricia Nguyen Department of Cardiology, Stanford University School of Medicine, Palo Alto, CA, USA, pknguyen1@yahoo.com

Francis G. O'Connor Department of Military and Emergency Medicine, Consortium for Health and Military Performance, Uniformed Services University of the Health Sciences, Bethesda, MD, USA, foconnor@usuhs.mil

David E. Price Department of Family Medicine, Carolinas Medical Center – Eastland, Charlotte NC, USA, david.price@carolinas.org

H. Jack Pyhel Department of Family Practice, University of South Florida Medical School at Bayfront Medical Center, St. Petersburg; Heart & Vascular Institute of Florida, St. Petersburg, FL, USA, Hjp@tampabay.rr.com

Vibhuti N. Singh Department of Medicine, Division of Cardiology, University of South Florida College of Medicine; Director, Clinical Research, Suncoast Cardiovascular Center, St. Petersburg, Florida, USA, vsingh@health.usf.edu or vnsingh@post.harvard.edu

Eric T. Warren Department of Family Medicine, Carolinas Medical Center – Eastland, Charlotte NC, USA, eric.warren@carolinas.org

Russell D. White Department of Community and Family Medicine, University of Missouri—Kansas City, Truman Medical Center Lakewood, Kansas City, MO, USA, Russell.White@tmcmed.org or jockdoc2000@hotmail.com

Part I
Performing the Exercise Test

Chapter 1
Exercise Physiology for Graded Exercise Testing: A Primer for the Primary Care Clinician

Francis G. O'Connor, Matthew T. Kunar, and Patricia A. Deuster

Exercise testing is an advanced clinical procedure used by providers to assess functional capacity for the purpose of guiding cardiovascular and pulmonary diagnoses and therapies. Numerous clinical guidelines, texts, and consensus statements have been published to assist clinicians in the identification of indications and criteria for treadmill stress testing, as well as procedures for test performance and interpretation [1–4]. However, the physiology of exercise testing, which is the foundation for exercise testing, is often overlooked in resource publications, as well as during the clinical training of providers. Education in exercise physiology is largely limited to the pre-clinical years, despite the fact that progress in cardiovascular exercise physiology is ongoing. This chapter functions as a primer for the primary care clinician who conducts exercise testing: core concepts pertaining to energy metabolism, skeletal muscle physiology, and cardiovascular and pulmonary physiology are reviewed. Additionally current concepts pertaining to testing for maximal aerobic power, factors that influence both test performance and results, and the physiology of myocardial ischemia and ST-segment depression are discussed.

Skeletal Muscle and Energy Production

Skeletal Muscle Physiology

The end-organ of exercise is skeletal muscle. Skeletal muscle can be subdivided anatomically into fascicles, which contain approximately 150 myofibers (muscle cells) (Fig. 1.1). Each muscle cell is composed of many myofibrils (5–10,000). Each myofibril in turn contains approximately 4,500 sarcomeres, which constitute

F.G. O'Connor (✉)
Department of Military and Emergency Medicine, Consortium for Health and Military Performance, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd., Bethesda, MD 20814, USA
e-mail: foconnor@usuhs.mil

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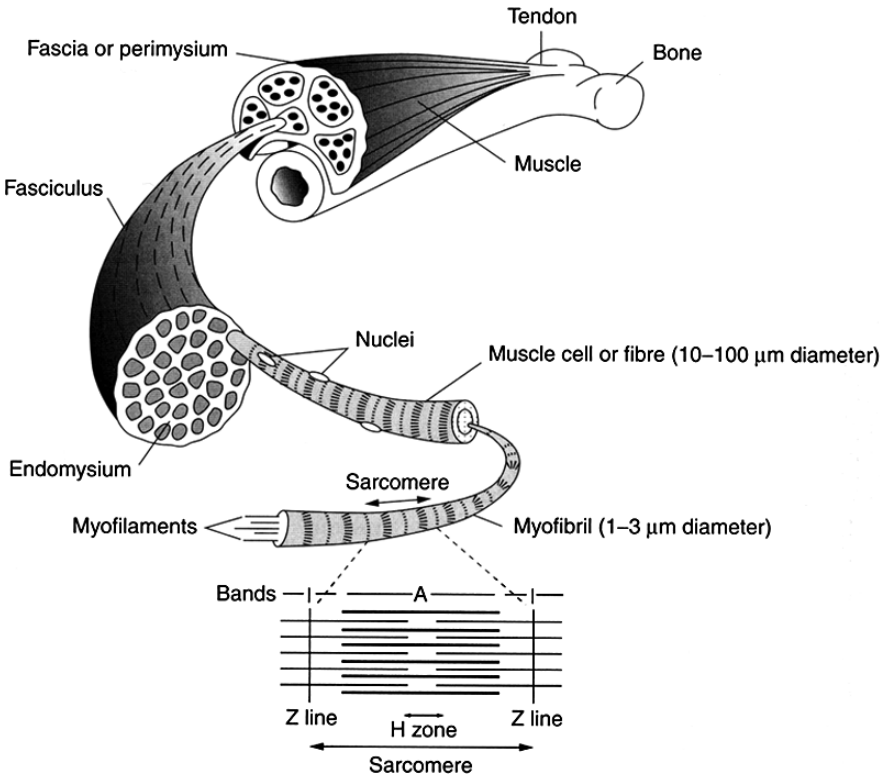

Fig. 1.1 Basic anatomy and structure of skeletal muscle physiology

the functional unit of the muscle cell. Sarcomeres are composed of two distinct myofilaments: thick and thin, with myosin and actin being the primary thick and thin myofilament proteins, respectively. Troponin, tropomyosin, titin, nebulin, and desmin are other important proteins that maintain the structure and function of the myofilaments.

Muscle Contraction

The dominant theory of muscle contraction is the sliding filament theory, which states that muscle contraction occurs when myosin heads bind to actin. The subsequent binding of adenosine triphosphate (ATP) to myosin breaks the actin–myosin bond and allows myosin to bind to another actin site farther along the thin filament. The process of myosin binding, releasing, and rebinding to actin forces the myofilaments to slide past each other in a ratchet-like fashion to create a series of cross-bridge linkages. This cross-bridging creates an oscillatory pattern with no more than 50% of the myosin heads attached to actin at any given moment.

Muscle Fiber Types

Skeletal muscle consists of two major fiber types: type I (slow twitch) and type II (fast twitch). Overall, type I fibers are characterized by lower force production, power, and speed, but greater endurance than type II fibers. Type I fibers have lower glycogen stores and myosin-ATP-ase activity and more mitochondria than their type II counterpart. The abundance of mitochondria and the high activities of enzymes involved in aerobic metabolism are associated with resistance to fatigue and ability to sustain submaximal activities. Type II muscle fibers, which can be classified into at least two other types (type IIa and type IIx), exhibit an approximately three to five times faster time to peak tension than type I fibers and are recruited preferentially during high-intensity exercise [5–12]. In fact, a hierarchical order of fiber activation with increasing intensity of exercise has been shown [13]. Type II fibers also have higher rates of cross-bridge turnover than type I fibers, and thus require more ATP per unit of time and are readily fatigued [5, 6]. Additionally, type II fibers exhibit greater activities of the enzyme lactate dehydrogenase (LDH) than type I fibers [14]. LDH, as discussed below, catalyzes the reversible reduction of pyruvate to lactate with accompanying oxidation of NADH to nicotinamide adenine dinucleotide (NAD+), in an effort to maintain ATP in the absence of oxygen.

The distribution of fiber types varies as a function of genetics and training. The proportions of type I and type II fibers in untrained persons are approximately 53 and 47%, respectively, whereas the proportion of type II fibers in resistance and endurance-trained individuals averages 67 and 50%, respectively [5, 6, 10–12]. The metabolic and mechanical profiles of fiber types can adapt in response to training, but the adaptations are training specific [11, 12].

Energy Metabolism

As indicated earlier, the process that facilitates muscular contraction is entirely dependent on the body's ability to provide and rapidly replenish ATP. Minimal amounts of ATP are stored for muscle contraction, but ATP can be derived from three specific energy systems: the immediate or creatine phosphate system; the short-term or glycolytic system; and the long-term or oxidative/aerobic system. Muscle fiber types at rest have intrinsically different contents of creatine phosphate (CP), ATP, and Inorganic Phosphate (Pi).

The immediate or phosphagen system consists of adenosine diphosphate (ADP), ATP, creatine (C), and CP. ATP is produced/regenerated when the enzyme creatine kinase catalyzes the transfer of phosphate from CP to ADP. Muscle fibers store approximately four times more CP than ATP, with type II fibers storing almost twice as much as type I fibers [15]. The CP system sustains energy during very short bursts of maximal power (Table 1.1).

The short-term or glycolytic system provides 1–1.6 min of energy for muscular activity. At the onset of any exercise, the oxygen demand is greater than the supply, so glucose from glycogen is converted to pyruvate for a net yield of 2 ATP. For glycolytic production of ATP to continue in the absence of oxygen, nicotinamide

Table 1.1 Energy systems

Energy systems	Mole of ATP per min	Time to fatigue
Immediate: phosphagen	4	5–10 s
Short-term: glycolytic	2.5	1–1.6 min
Long-term: aerobic	1	Unlimited

adenine dinucleotide (NADH), an important coenzyme, must reduce pyruvate to lactate to regenerate NAD+ [16]. It is the regeneration of NAO+ that allows glycolytic production of ATP to continue. ATP synthesis through this anaerobic system is inefficient in that it yields only 2 ATP per molecule of glucose in contrast to 36 ATP from oxidative metabolism of glucose. Exercise at near maximal intensities results in a rapid breakdown of muscle PCr, predominantly in type IIx fibers [8]. In contrast, glycogen appears to be depleted similarly in type I and type II fibers at maximal intensities, but preferentially in type I fibers after submaximal exercise [17,18]. This evidence demonstrates the importance of type II fibers in maximal force generation.

The long-term or oxidative/aerobic system involves two major fuels: carbohydrates, in the form of glucose, and free fatty acids (FFA). At rest and during submaximal exercise both carbohydrates and FFA contribute to ATP synthesis. Although FFA are a more efficient source of energy (they yield 8 ATP per carbon compared to only 6.3 ATP for glucose) than carbohydrates, glucose is more readily available and can be metabolized more rapidly than FFA to generate ATP. Glucose can be stored as glycogen in liver and muscle and is readily available for energy; alternatively, glucose can be used in the synthesis of fatty acids and stored as triacylglycerol, primarily in adipocytes. Triacylglycerols must be hydrolyzed to release the free fatty acids before being available for energy.

Aerobic energy production takes place within the mitochondria. If pyruvate formed in the cytoplasm crosses the mitochondrial membrane, it is oxidized to acetyl coenzyme A (acetyl CoA), which enters the tricarboxylic acid (TCA/Krebs) cycle where it is oxidized to carbon dioxide. In the process three molecules of NADH and one molecule of reduced flavin adenine dinucleotide ($FADH_2$) are produced. It is these reduced coenzymes that present electrons to the electron transport chain to generate ATP in the mitochondria. As noted above, one molecule of glucose ultimately contributes a total of 36 ATP. Free fatty acids are sequentially oxidized to yield acetyl CoA, which enters the TCA cycle as noted above.

Acute Exercise and the Cardiopulmonary Response

Cardiovascular Physiology

The principal function of the cardiovascular system during exercise is to sustain delivery of oxygen (O_2) and vital nutrients to the target organ, skeletal muscle. The cardiovascular system consists of a pump, a high-pressure distribution circuit, exchange vessels, and a low-pressure collection and return circuit [19]. This system

moves approximately 5 liters (L) of blood each minute at rest, so the heart pumps nearly 7,200 L (1,900 gallons) per day. The cardiovascular system's productivity can increase more than four to eight times ($\sim$40 L min^{-1}) above resting levels during strenuous exertion in the upright position, as a result of changes in heart rate, stroke volume, and peripheral resistance.

Maximal Oxygen uptake ($VO_{2\,max}$) is considered the "gold standard" of cardiopulmonary health and represents the body's ability to deliver and utilize oxygen. $VO_{2\,max}$ is a product of cardiac output and extraction of oxygen from the circulation by the peripheral skeletal muscles; $VO_{2\,max}$ is conveniently expressed by the Fick equation:

$VO_{2\,max}$ = Maximal cardiac output × Maximal arteriovenous oxygen difference

Maximal cardiac output = Heart rate$_{MAX}$ × Stroke volume$_{MAX}$

Maximal arteriovenous oxygen difference = Capillary arterial O_2 − Capillary venous O_2

The volume of blood moved by cardiac activity each minute is termed *cardiac output* and is typically expressed in L min^{-1}. Cardiac output is a function of heart rate (beats min^{-1}, bpm) and stroke volume (mL beat^{-1}) and is the principal, or central, component of an individual's $VO_{2\,max}$. The ability of the working muscles to extract oxygen from the blood is the peripheral component of $VO_{2\,max}$ determination; it is calculated from the arteriovenous oxygen difference (a – vO_2). Each component of the Fick equation is critical to the performance and understanding of the exercise stress test and is subsequently reviewed in detail and summarized in Fig. 1.2.

$VO_{2\,max}$

By definition, *maximal oxygen uptake*, $VO_{2\,max}$, is the highest oxygen uptake (VO_2) achieved when a person is working at maximal capacity. Classically, VO_2 reaches a plateau and does not increase further, even with an increase in external workload. Absolute values, typically expressed in L min^{-1}, may range from as low as 1.0 L min^{-1} (or lower in persons with cardiovascular disease) up to 6 L min^{-1} (or possibly higher in large, well-trained individuals). One of the most predictable relationships in exercise physiology is that between oxygen uptake and cardiac output: VO_2 is directly related to cardiac output (Fig. 1.2) [4, 20].

Because two individuals of quite different sizes may have the same absolute values for $VO_{2\,max}$ it is often normalized for body weight to allow for between-subject comparisons. The most familiar unit of expression is milliliter (mL) kilogram (kg)$^{-1}$ min^{-1}. Values for $VO_{2\,max}$ range from a low of 10 to a high of 80^{+} mL kg^{-1} min^{-1}. For example, if two men both have absolute values of 4.2 L min^{-1} and one weighs 70 kg and the other 95 kg, then their $VO_{2\,max}$ values relative to body weight would be 60 mL kg^{-1} min^{-1} for the 70-kg man and 44.2 mL kg^{-1} min^{-1} for the 90-kg man. This relative $VO_{2\,max}$ provides an indication of an individual's potential for

work, particularly running, swimming, cycling, and overall endurance. Clearly the man who weighs only 70 kg is in better shape for physical work because he could work with less relative effort at 40 mL kg^{-1} min^{-1} than the 90 kg man (66 vs. 90% of $VO_{2\,max}$).

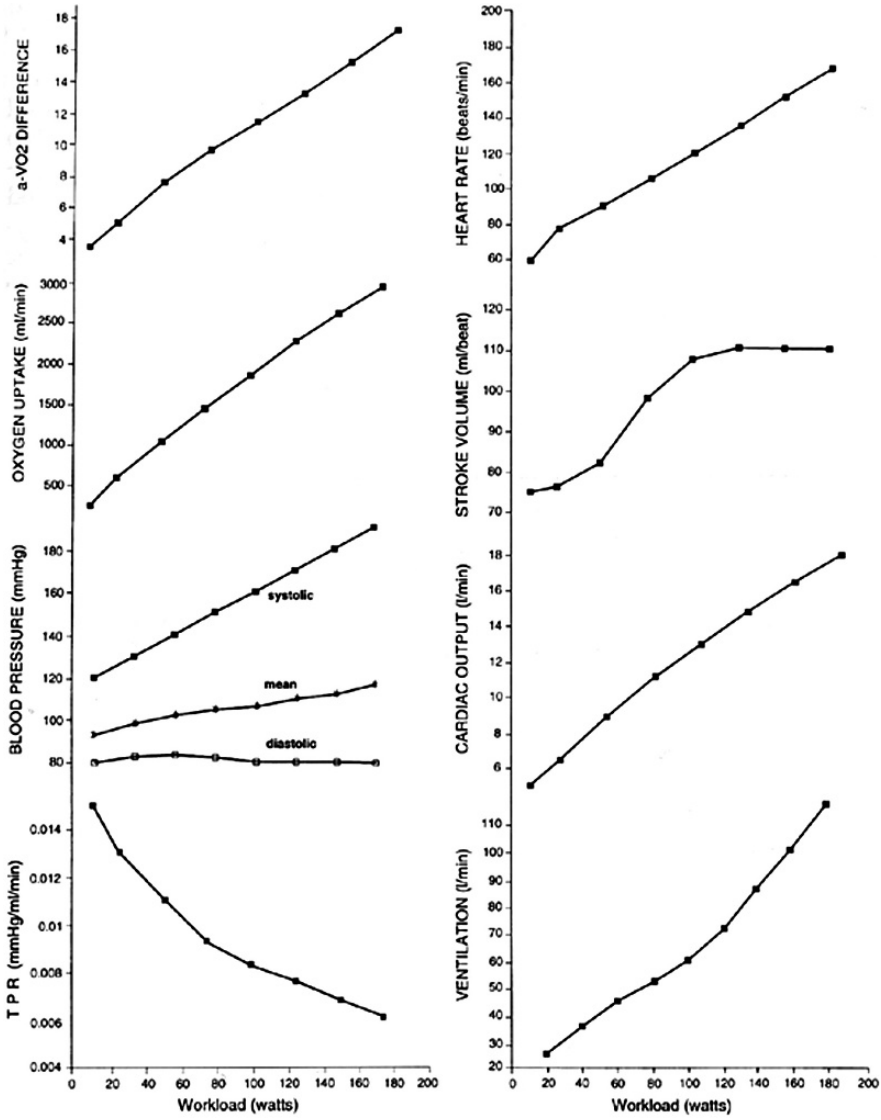

Fig. 1.2 Basic hemodynamic and metabolic variables and the magnitude of the response from rest to a moderately high level of exercise. TPR = total peripheral resistance. Units for a–VO_2 difference are mL O_2 per 100 mL blood. (From Myers JN. The physiology behind exercise testing. *Primary Care* 2001;28:5–14, with permission of Elsevier.)

VO_2, in addition to being normalized by weight, can also be normalized clinically. In the clinical setting VO_2 is normalized to metabolic equivalents (METs), which represent a multiple of an average value of resting energy expenditure of 3.5 mL kg^{-1} min^{-1}. The VO_2 above rest required to perform recreational or occupational work can then be represented by the number of METs for a given activity. The determination of maximal MET capacity can be of use when risk-stratifying patients for clinical decisions. Most activities of daily living require less than 4 METs; patients with coronary artery disease or congestive heart failure who perform below this level have a guarded prognosis. In contrast, the ability to exercise at 10 METs without ischemia places the patient at low risk, with a 1-year mortality of <2% [21]. A maximal exercise capacity of 13 METs, regardless of other factors to include the presence and extent of ischemia, predicts an excellent short-term prognosis.

The American College of Sports Medicine (ACSM) has published normative values for $VO_{2\,max}$ by age and gender so that individual values can be classified into one of five groups: poor (well below average), fair (below average), average, good (above average), and excellent (well above average) [4] (Table 1.2). The importance of $VO_{2\,max}$ cannot be overemphasized with respect to health: low aerobic power, or low cardiovascular fitness, is associated with higher morbidity and earlier mortality for all causes [22]. Data from 1999–2000 to 2001–2002 National Health and Nutrition Examination Surveys (NHANES) showed that approximately 11.3% of non-Hispanic whites and 22.9% of non-Hispanic blacks between 20 and 49 years of age had estimated $VO_{2\,max}$ values in the ACSM's poor category (below 30 mL kg^{-1} min^{-1}) [23]. Non-Hispanic black women had the lowest $VO_{2\,max}$ values such that 30.9% were in the poor category. Of note is the finding that 33.6% of adolescents have poor aerobic fitness [24]. Thus, despite the importance of maximal aerobic power, the distribution of estimated $VO_{2\,max}$ values from NHANES indicates low fitness among most of the US population.

Table 1.2 Normative values (percentile) for maximal aerobic power for men and women by age*

Age	Poor (≤10)	Fair (10–30)	Average (30–70)	Good (70–90)	Excellent (≥ 90)
			Men		
20–29	< 35	35–41	42–49	50–55	> 55
30–39	<33	33–39	40–47	48–52	> 52
40–49	<31	31–36	37–45	46–51	> 51
50–59	<30	30–35	36–41	42–49	> 49
≥ 60	<27	27–31	32–37	38–44	> 44
			Women		
20–29	< 28	28–33	34–41	42–49	> 49
30–39	<27	27–31	32–39	40–46	> 46
40–49	<25	25–30	31–36	37–43	> 43
50–59	<22	22–27	28–33	34–38	> 38
≥ 60	<20	20–23	24–31	32–35	> 35

*American College of Sports Medicine Aerobic Power Standards for men and women. Reprinted with permission from LLW.

Heart Rate

The cardiovascular control center that regulates heart rate, as well as stroke volume and the peripheral redistribution of blood to working muscle, is located in the ventrolateral medulla. Anticipation of exercise is processed in the brain and results in an inhibition of parasympathetic activity and an increase in sympathetic outflow, with cardio-acceleration actually preceding the onset of voluntary muscle contraction [25]. In addition to acceleration of heart rate, these neural activation responses result in a series of cardiovascular responses: increased myocardial contractility; vasodilation in skeletal muscle; vasoconstriction in non-exercising areas (e.g., gut); and an increase in arterial blood pressure. The redistribution of cardiac output to exercising muscle can be quite impressive, with greater than 85% of total blood flow directed to the skeletal muscle with peak exercise.

Heart rate acceleration with exercise is subject to a number of intrinsic and extrinsic factors, including age, fitness level, the presence of cardiac disease, blood volume, the type of activity, body position, and the environment. Maximum heart rate can be estimated from the formula 220 – age in years; however, there is a wide variation in maximal heart rate capability, with one standard deviation of 10–12 bpm. In addition, maximum heart rate and cardiac output are generally decreased in older individuals, secondary to intrinsic cardiac changes, including decreased beta-adrenergic responsivity [26,27]. Therefore, although the age-predicted maximum heart rate is a useful measurement for an initial estimation, the large standard deviation limits the usefulness of this parameter in estimating the exact age-predicted maximum for an individual patient [28]. In general, maximal heart rate is generally unchanged by exercise training, while resting heart rate frequently decreases with aerobic training, secondary to an enhanced vagal tone.

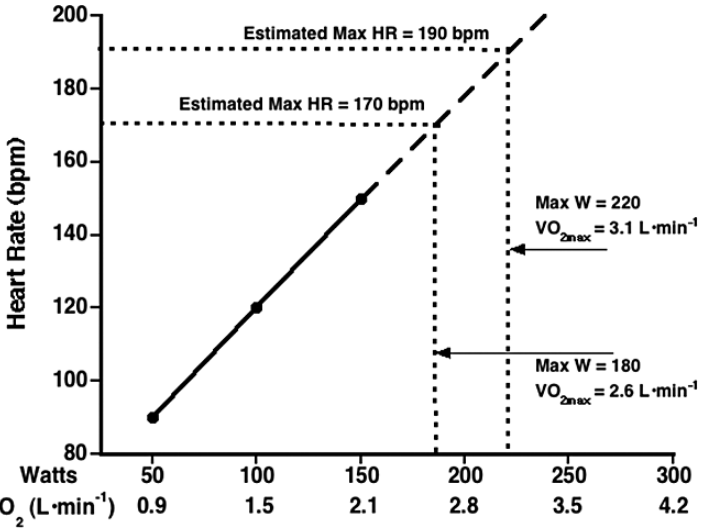

Fig. 1.3 The relationship between heart rate and $VO_{2\,max}$

Fitness level is also directly related to heart rate at a given workload. Individuals who are more fit and have a higher intrinsic $VO_{2\,max}$ can accomplish comparable workloads with lower heart rates. A trained runner may be able to run 6 mph on a treadmill at a heart rate of 110 bpm, whereas a less fit person may require a corresponding heart rate of 150 bpm to run at the same pace. The ability to produce a cardiac output to meet the demands of comparable workload and oxygen requirement is explained by the Fick equation: the well-trained runner has the advantage of a training-induced increase in stroke volume and more efficient peripheral extraction of oxygen by exercising muscle than the less fit non-runner.

Heart rate is known to increase with increasing VO_2. Åstrand and Ryhming were among the first to report this linear relationship between heart rate and VO_2 and, based on this relationship, recommended the use of heart rate to predict $VO_{2\,max}$ (Fig. 1.3) [29]. Because heart rate in a trained athlete can go from a resting rate of 40 bpm to over 200 bpm, heart rate is the principal driver for the increase in cardiac output.

Stroke Volume

The second principal component of cardiac output that changes with exercise is stroke volume. Enhanced sympathetic activity increases not only heart rate, which provides a chronotropic stimulus, but also an inotropic stimulus, which increases myocardial contractility. Stroke volume is determined by subtracting the volume of blood in the left ventricle at end-systole from that identified at end-diastole. Normal values for stroke volume range from 75 to 100 mL $beat^{-1}$, which can nearly double with exercise. Factors that can affect an individual's stroke volume include genetics (e.g., heart size); conditioning (e.g., contractility, preload, and afterload); and disease (e.g., valvular and wall motion abnormalities).

Filling pressure is instrumental in augmenting cardiac output by increasing the end-diastolic volume. The Frank–Starling law of the heart states that the force of contraction of cardiac muscle remains proportional to its initial resting length. As cardiac preload increases with an increased venous return, a more forceful contraction results. During exercise, stroke volume is principally augmented by increasing end-diastolic volume and reducing peripheral vascular resistance, which decreases cardiac afterload. Maximal stroke volume is achieved at relatively low exercise intensities, as pericardial constraint serves to limit left ventricular end-diastolic volume. Increasing cardiac output becomes dependent on an increase in heart rate.

Cardiac contractility also contributes to the increase in stroke volume, but not to the extent seen with changes in end-diastolic volume. Increasing cardiac contractility reduces end-systolic volume by increasing ejection fraction and thereby increasing stroke volume. Increased cardiac contractility has been observed in healthy hearts, whereas subjects with coronary artery disease or congestive heart failure have less predictable responses and may actually demonstrate increasing end-systolic volumes with an increasing exercise demand.

Cardiac afterload is a measure of the force required to eject blood from the heart into the peripheral circulation. An increase in afterload, or peripheral resistance,

can result in a decreased ejection fraction. Systolic blood pressure represents the force of the blood against the arterial walls with ventricular contraction, whereas diastolic blood pressure reflects peripheral resistance during the relaxation phase of the cardiac cycle. During dynamic exercise, total peripheral resistance is normally decreased as a result of vasodilation of the skeletal muscle vasculature. Accordingly, despite a marked increase in cardiac output with peak exercise and a clear rise in systolic blood pressure, mean arterial pressure increases only moderately (Fig. 1.2).

Arterial-Venous Oxygen Concentration Difference

The peripheral contribution to $VO_{2\,max}$ is the difference between the O_2 concentration of the arteries and veins ($a - vO_2$). At rest the ($a - vO_2$) is typically 4–5 mL O_2 per 100 mL, which equates to 23% extraction. During dynamic exercise, this difference can increase as exercising muscle extracts oxygen more efficiently. At peak exercise the ($a - vO_2$) may reach 18 mL O_2 per 100 mL, which is approximately 85% extraction [30]. In general, the ($a - vO_2$) difference or the percent O_2 extracted does not explain differences in $VO_{2\,max}$ between subjects who are relatively homogeneous; the ($a - vO_2$) difference appears to increase by a relatively fixed amount during exercise, such that differences in $VO_{2\,max}$ are principally explained by changes in cardiac output [30]. This observation supports the conclusion that O_2 supply, not muscle use, limits aerobic capacity.

Many factors can alter the ($a - vO_2$) difference. Hemoglobin concentration, alveolar ventilation, partial pressure of O_2, and pulmonary diffusion capacity are important for the arterial component. In addition, the ($a - vO_2$) difference is altered by conditions that shift the O_2 dissociation curve to the left, such as decreased carbondioxide (CO_2), decreased temperature, decreased 2,3-diphosphoglycerate (2,3-DPG), and an increased pH. Any increase in the affinity of O_2 for hemoglobin will reduce the O_2 released to the tissue at a given partial pressure of O_2. In contrast, conditions that shift the O_2 dissociation curve to the right (an increase in 2,3-diphosphoglycerate or temperature, a decreased pH) allow greater O_2 dissociation at the tissue level and thereby augment extraction [19]. It is important to note that arterial hemoglobin and O_2 saturation levels in healthy adults remain similar throughout exercise to resting levels.

As previously discussed, the ability to extract O_2 is not altered significantly by aerobic training. However, training appears to increase muscle capillary density, which serves to increase blood flow to working muscles. Studies have demonstrated that fit individuals have a tremendous ability to alter blood flow to exercising muscle and tend to have a greater muscle capillary density, which in turn facilitates greater oxygen delivery to working muscle [31].

Pulmonary Physiology

Exercise performance is dependent on the body's ability to deliver O_2 to the target organ of exercise, skeletal muscle. The ability to perform physical work is depen-

dent upon a number of factors, with the initial step accomplished by the pulmonary system. The transport of O_2 from the external environment to the lung is a carefully orchestrated process, wherein air is ventilated from the lungs to the alveolus and O_2 diffuses across a pulmonary membrane to bind with hemoglobin, which resides inside a red blood cell traveling through a pulmonary capillary.

The cornerstone of understanding pulmonary aspects of exercise testing and physiology is a clear understanding of the nomenclature. The amount of air moving in and out of the lung per minute is defined as minute ventilation (VE). VE is a function of tidal volume (VT) and respiratory rate and is expressed in L min^{-1}. Maximal voluntary ventilation (MVV), a measure of the maximum breathing capacity, is the volume of air exchanged during repeated maximal respirations in a specified period of time; it too is expressed in L min^{-1}. The ventilatory threshold is defined as the point where ventilation increases disproportionately to VO_2.

Strenuous work requires the pulmonary system to move massive amounts of air into and out of the lungs. Accordingly there is an increase in the end-inspiratory and a decrease in the end-expiratory lung volume. In highly fit individuals, VE has been shown to increase from approximately 8 to 12–150 L min^{-1} at peak exercise. Pulmonary blood flow also increases two- to fourfold during exercise with a small increase in pulmonary artery pressure. These changes in flow and pressure are associated with significant reductions in pulmonary vasculature resistance.

Testing for Maximal Aerobic Power

Maximal aerobic power, or maximal oxygen uptake ($VO_{2\,max}$), is a measure of the maximum amount of oxygen that an individual can use per unit of time during strenuous physical exertion at sea level. It is an important measure for several reasons: (1) it serves as an index of cardiovascular and pulmonary function; (2) it characterizes the functional capacity of the cardiopulmonary system to transport oxygen to the working muscles; and (3) it is one of the limiting factors in endurance performance. An individual's $VO_{2\,max}$ can be estimated by a variety of techniques to include treadmill running, cycle ergometry, arm cranking, stair stepping, rowing, or walking. However, the gold standard is progressive treadmill testing by running to exhaustion. The most common way to measure $VO_{2\,max}$ is by open-circuit spirometry, whereby the individual breathes in ambient air and the exhaled air is measured and analyzed. The amount of oxygen consumed (VO_2) can be computed based on knowing the composition of the inspired air and by quantifying the volume (V) and oxygen (O_2) content of the expired air.

When a maximal aerobic power test is conducted, it is important to document whether a true $VO_{2\,max}$ has been achieved. Such a determination begins with understanding the physiologic responses to severe exercise and assessing selected parameters that have been designated as criteria for a $VO_{2\,max}$ test. The criteria allow the tester to decide whether the obtained value should be considered $VO_{2\,max}$ or a peak VO_2 (VO_{2peak}). As noted above, a plateau in VO_2, or only a small increase

in VO_2 with an increase in external workload, is considered the primary criterion. Secondary criterion includes measures of blood (or plasma) lactate, respiratory exchange ratio (RER), heart rate, and perceived exertion [4, 32, 33].

Criteria for Maximal Aerobic Power

A Plateau in Oxygen Uptake

A plateau in oxygen intake, despite an increase in workload, is considered the primary criterion for $VO_{2\,max}$. If a plateau in VO_2 is observed, $VO_{2\,max}$ has been achieved. However, this criterion is not always achieved. Various factors influence quantification of $VO_{2\,max}$, to include between-subject variability and absolute increases in grade and speed. Meyers et al. [34] suggested that a plateau phenomenon is not always seen with various protocols because of the sampling interval selected (e.g., breath-by-breath, 5, 10, or 15 s averages) and magnitude of work increments for each exercise stage. Many efforts have been undertaken to define a precise criterion for attaining a plateau. In one of the early studies, performed by Taylor et al., 115 subjects ran at a speed of 7 mph on a given grade (0–12.5%) for 3 min; the grade was increased 2.5% until the subject could go no longer; grade increases were typically carried out on different days or after a period of rest [35]. With this protocol, they showed that a 2.5% grade increase typically resulted in a rise of approximately 300 mL min^{-1} in VO_2. However, at a certain point, higher levels of exercise, which were different for each person, did not elicit the 300 mL min^{-1} increase. Based on this information, it was determined that an increase of less than 150 mL min^{-1} or 2.1 mL kg^{-1} min^{-1} in VO_2 at the next higher work rate marked a plateau. They concluded that a grade increase was preferable to speed increases for achieving a plateau. Further, they demonstrated that 93.9% of persons tested achieved the designated plateau [35].

Importantly, other investigators have not always found that such a high percentage of persons achieve plateau. The percentage of adults achieving plateau ranges from 25% of men and women to 72.5% of men [36–38]. The numbers are similar for children with 25–33% of prepubertal children achieving a plateau during treadmill exercise and cycle ergometry, respectively [37, 39]. For most studies, VO_{2peak} values do not differ from $VO_{2\,max}$ values. Thus, although a plateau is not seen in many people, due to various factors, VO_{2peak} may be considered a valid index of $VO_{2\,max}$. Although no consensus has been reached over the years, this criterion is still considered by many to be the gold standard or the primary criterion. Because a plateau is not consistently observed, secondary criteria described below have evolved.

Blood Lactate Levels

In the absence of a true plateau in VO_2, a rise in blood lactate has been used to demonstrate a maximal effort [4, 40]. As the workload continues to rise and the person nears a maximal effort, blood lactate levels increase due to accelerated glycol-

ysis, an increase in the recruitment of fast-twitch muscle fibers, a reduction in liver blood flow, and/or an elevation in plasma epinephrine concentration [3, 14, 40, 41]. These observations were first made by Åstrand, who noted that in the absence of a visible plateau, lactate values, along with a subject-reported stress level, could be used to document attainment of a true $VO_{2\,max}$ [40, 42].

Although identifying a standard cutoff for blood lactate levels has been difficult, the values derived from Åstrand's earliest studies suggesting a cutoff of 7.9–8.4 mmol L^{-1} are still accepted today [40, 42]. Subsequent investigators have noted that 8 mM is a reasonable criterion value [32,33,43,44]. Cumming and Borysyk [43] and Stachenfeld [44] found that 78% of their test subjects achieved lactate levels greater than 8 mmol L^{-1}. Moreover, 8 mmol L^{-1} was the best criterion in terms of specificity and positive predictive value as compared to other secondary criteria [44]. Current standards vary, but a value greater than or equal to 8 mmol L^{-1} appears to be consistent with research studies and is well accepted by researchers in general.

Respiratory Exchange Ratio

The respiratory quotient (RQ) and respiratory exchange ratio (RER) are both calculated as the ratio of the volume of CO_2 produced to the volume of O_2 used, or VCO_2/VO_2. The RQ, which typically ranges between 0.7 and 1.0, is an indicator of metabolic fuel or substrate utilization in tissues; it must be calculated under resting or steady-state exercise conditions. A ratio of 0.7 is indicative of mixed fat utilization whereas a ratio of 1.0 indicates exclusive use of carbohydrates [45]. Thus, during low-intensity, steady-state exercise, the RQ and RER are typically between 0.80 and 0.88, when fatty acids are the primary fuel.

As the intensity of the exercise increases, and carbohydrate becomes the dominant or primary fuel, the RQ and RER increase to between 0.9 and 1.0. Because the RQ reflects tissue substrate utilization, it cannot exceed 1.0. In contrast, the RER, which reflects respiratory exchange of CO_2 and O_2, commonly exceeds 1.0 during strenuous exercise. During non-steady-state strenuous exercise, the volume of CO_2 production rises because of hyperventilation and increased buffering of blood lactate derived from skeletal muscles; thus, RER no longer reflects substrate usage, but rather high ventilation rates and blood lactate levels [33, 42, 45].

Because RER reproducibly increases during exercise, it is considered a parameter that can document maximal effort. Issekutz, the first to propose the use of RER as a criterion for $VO_{2\,max}$, noted that it must exceed 1.15 [45]. A higher value may suggest a more accurate assessment of $VO_{2\,max}$. The 1.15 value appears to be reasonable, although not all persons are able to achieve it. Studies have noted values of 1.00, 1.05, 1.10, and 1.13 as criterion for maximal performance, but at present no clear consensus has been reached [32, 33].

Age-Predicted Maximal Heart Rate

The widely recognized linear relationship between heart rate and VO_2 has encouraged the use of estimated maximal heart rate as a criterion for achieving $VO_{2\,max}$. Attaining a target percentage of the age-predicted maximal heart rate is one of the

most widely recognized criterion [32]. Unfortunately, the traditional equation used to estimate maximal heart rate (220 – Age) was derived from approximately 10 different studies and most of these studies tested subjects younger than 65 years [28]. Additionally, the equation was never validated for adults over 60 years, and thus, it may underestimate maximal heart rate in older adults by more than 20 bpm. For this reason, the ACSM and others have recommended that heart rate should not be used alone, but rather in combination with other secondary criteria [4, 32, 33]. In 2001, Tanaka et al. published a new equation for estimating age-predicted maximal heart rate (208 – 0.7 × Age), but whether it will prove to be less variable at all ages remains to be determined [28].

Borg Scale or Rating of Perceived Exertion

The Borg scale is the most widely used method for quantifying perceived exertion. It was designed to increase in a linear fashion as exercise intensity increased and parallel the apparent linearity of VO_2 and heart rate with work load [46, 47]. The original Borg scale ranges from 6 to 20, with each number anchored by a simple and understandable verbal expression. The specific numbers of the scale were intended to be a general representation of actual heart rate, such that when a person was exercising at 130 bpm, a perceived exertion of 13 should be reported. Similarly, if the perceived exertion were 19, a heart rate of around 190 would be expected. The scale was not intended to be exact, but rather an aid in the interpretation of perceived exertion.

Studies have demonstrated a good correlation between RPE and VO_2 [48, 49]. Eston et al. [48] obtained RPE values during a graded exercise test and reported a good correlation between heart rates and VO_2 when the reported RPE was between 13 and 17. An RPE value of 17 or greater should be accepted as meeting the criterion for achieving $VO_{2\,max}$.

Since the initial scale was developed, a variant scale that uses 0–10 as the numeric ratio has been proposed. This non-linear scale, which has not been widely accepted, is suitable for examining subjective symptoms, such as breathing difficulties [46]. However, the original 15-point RPE scale remains the standard for use as a criterion for $VO_{2\,max}$.

Recommended Criteria for Testing

The criteria for $VO_{2\,max}$ were initially established for a discontinuous treadmill test that used 2.5% increases in grade. To date, the criteria for a plateau have not been redefined for other specific tests, but the 150 mL min^{-1} increase continues to be used. Since attainment of a true plateau is not an absolute prerequisite, some combination of secondary criterion may be preferable. The criteria presented in Table 1.3 are offered as a guide, and it is suggested that three of the four secondary criteria be met. If a true plateau is noted, then this alone would be sufficient for documenting $VO_{2\,max}$. If the criteria are not met, then the test would be considered VO_{2peak}.

Table 1.3 Criteria for documenting a maximal effort test*

↑ in VO_2 < 150 mL•min^{-1} or 2.1 mL•kg^{-1}•min^{-1} with a 2.5% grade ↑
Blood lactate ≥ 8 mmol L^{-1}
RER ≥ 1.15
↑ in HR to maximal estimated for age ± 10
Borg scale ≥ 17

* If the first criterion is not met, then at least three of the remaining four should be met.

Factors Affecting Maximal Exercise Performance

Intrinsic Factors

Although many factors determine exercise capacity, the most influential intrinsic factors that influence maximal exercise performance are age, gender, and genetics. Clearly age is one of the most important predictors of exercise capacity. Age is inversely related to $VO_{2\,max}$: $VO_{2\,max}$ declines approximately 10% per decade in the absence of regular activity. Regular aerobic exercise can assist in attenuating this decline. Women tend to have lower $VO_{2\,max}$ levels when compared to men; values are approximately 15% lower even when matched by activity status. Lower values reflect intrinsic differences in body composition, including a greater percent body fat, less muscle mass, smaller hearts, lower vital capacity and lower hemoglobin levels. Genetic endowment may be an important predictor of performance, as both $VO_{2\,max}$ and skeletal muscle adaptations to training appear largely genotype dependent [50].

Extrinsic Factors

In addition to individual intrinsic factors, extrinsic factors, including type of exercise, environment, and postural position can significantly affect performance. $VO_{2\,max}$ is highly dependent on the quantity of skeletal muscle engaged during the exercise. Studies have demonstrated that exercise performed on a treadmill elicits higher $VO_{2\,max}$ values than those elicited by cycle or arm ergometry. However, the specificity of the test is also important: higher $VO_{2\,max}$ values are achieved in swimmers and cyclists when tested while swimming and cycling, respectively. In contrast, persons who have never cycled will typically not do as well on a cycle ergometer as on a treadmill.

Environmental extremes can challenge peak exercise performance; heat and cold produce competing demands for blood flow to accommodate temperature control, whereas altitude compromises peak performance through lower partial pressures of oxygen. Supine and upright exercise can produce significantly different results; upright exercise tends to be more familiar and produces a greater driving force for tissue perfusion, whereas exercise in the supine position elicits higher stroke volumes and cardiac output. These are just a few of the extrinsic factors to be discussed. Others include dietary supplements, prescription medications, clothing, and the like.

Physiology of Ischemia

Myocardial Oxygen Uptake

In order to meet the increasing O_2 demands of external work, the heart must correspondingly increase its own O_2 requirements. The increase in the internal work of the heart is identified as myocardial oxygen uptake (MO_2). Although direct measurements can only be performed in a laboratory setting, MO_2 can be estimated by multiplying systolic blood pressure by heart rate to yield the "double product" or "rate pressure product". The O_2 supply to the heart is augmented primarily by increasing coronary blood flow.

A healthy heart has the capacity to augment coronary blood flow at least fivefold, principally through vasodilation of large and small arterioles. This "coronary flow reserve" is the principal determinant of whether or not the exercise load will result in myocardial ischemia. Ischemia will ensue when the ability of the coronary arteries to augment coronary blood flow is compromised, e.g., atherosclerosis.

ST-Segment Depression

The principal indicator of myocardial ischemia during a graded exercise test is the presence of ST-segment depression. The phenomenon of ST-segment depression reflects an imbalance between myocardial O_2 supply and demand. The normal myocardial action potential has four distinct phases (Fig. 1.4). The fast depolarization (phase 0) is shown by the abrupt upstroke, which is related to the rapid entry of sodium (Na^+) into the cell through the fast Na^+-channels. The fast Na^+-influx initiates atrial, ventricular, and Purkinje action potentials. Phase 0 is terminated at about +30 mV when the fast Na^+-channels are inactivated/closed because of voltage threshold. Phase 1 marks the early repolarization from the upstroke due to potassium (K^+)-outflow. Phase 2 designates the plateau of the action potential, wherein the slow calcium (Ca^{2+})-Na^+-channels remain open for up to 300 ms. Phase 3 is the terminal repolarization and occurs when all the K^+-channels open so that large amounts of K^+ can diffuse out of the ventricular fibers. Phase 4 is recognized by restoration of the resting membrane potential to – 90 mV. This is brought about by the Na^+-K^+ pump, which restores ionic concentrations by exchanging Na^+ for K^+ in a ratio of 3:2.

Ischemia, with a resultant change in deflection of the ST-segment, reflects complex alterations in the electrical properties of the myocardial cell. Under normal conditions, the ST-segment is isoelectric since all myocardial cells repolarize at the same rate to the same resting potential. Ischemia causes a loss of the resting membrane potential, a shortened duration of repolarization, and a decrease in the amplitude and rate of rise for the action potential of phase 0 (Fig. 1.4) [51]. These changes create a voltage gradient between normal and abnormal myocardial cells

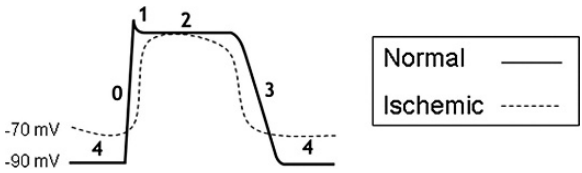

Fig. 1.4 Ventricular ischemia may alter the myocardial action potential by creating a lower resting membrane potential, decreased amplitude of phase 0, and an abbreviated repolarization in phases 2 and 3. The differential repolarization patterns between the epicardium and the endocardium can result in shifts in the ST-segment. (Adapted from Mirvis DM GA. Electrocardiography. In Zipes DP LP, Bonow RO, Braunwald E, ed., *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia: Elsevier; 2005, with permission of Elsevier.)

that leads to changes in repolarization of the cardiac vector and resultant changes in ST-segment deviation on the surface electrocardiogram.

Summary

Exercise testing is an invaluable tool for the primary care clinician. This resource provides a wealth of clinical information pertaining to the cardiopulmonary system, in particular, about how to identify patients with potential heart disease. Knowledge of exercise physiology and its application allows the clinician to create a more accurate picture of the patient's cardiovascular health. In turn, the clinician should be able to more accurately diagnose and manage the patient in health and disease.

References

1. Gibbons RJ, Balady BG, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing. Summary article: A report of the ACC/AHA task force on practice guidelines. J Am Coll Cardiol 2002;40:1531.
2. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Pina IL, Rodney R, Simons-Morton DA, Williams MA, Bazzarre T. Exercise standards for testing and training: A statement for healthcare professionals from the American Heart Association. Circulation 2001;104:1694–740.
3. Balady GJ, Berra KA, Golding LA, editors. ACSM's Guidelines for Exercise Testing and Prescription. 6th ed. Philadelphia: Lippincott, Williams & Wilkins; 2000.
4. Whaley MH, Brubaker PH, Otto RM, editors. ACSM's Guidelines for Exercise Testing and Prescription. 7th ed. Baltimore: Lippincott, Williams & Wilkins; 2006.
5. Tesch PA, Thorsson A, Essen-Gustavsson B. Enzyme activities of FT and ST muscle fibers in heavy-resistance trained athletes. J Appl Physiol 1989;67:83–7.
6. Li JL, Wang XN, Fraser SF, Carey MF, Wrigley TV, McKenna MJ. Effects of fatigue and training on sarcoplasmic reticulum Ca(2+) regulation in human skeletal muscle. J Appl Physiol 2002;92:912–22.
7. Beltman JG, de Haan A, Haan H, Gerrits HL, van Mechelen W, Sargeant AJ. Metabolically assessed muscle fibre recruitment in brief isometric contractions at different intensities. Eur J Appl Physiol 2004;92:485–92.