Cardiopulmonary Exercise Testing

Edited by

Alan R. Leff, M.D.

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Associate Professor
Section of Pulmonary and Critical Care Medicine
and Committee on Clinical Pharmacology
Director, Pulmonary Medicine Service
Pulmonary Function and Exercise Physiology
Laboratories Division of the Biological Sciences
The University of Chicago

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Preface

Exercise is a complex, multi-organ process involving the central nervous system, the motivation and command center, and the musculoskeletal system, which provides power output. The function of the pulmonary and cardiovascular systems is to supply nutrients in the required amounts to the organ systems engaged in locomotion. From this perspective, the highly channeled, organ-specific approach of the clinical subspecialist seems unnecessarily restrictive, and the risk that a clinically important problem will be missed is substantial if abnormal exercise performance is approached solely from the perspective of one clinical subspeciality. The objective of this book is to emphasize the need for an integrated approach involving both basic scientists and diverse clinical specialists in the clinical evaluation of exercise performance. Contributors include both basic and clinical scientists, and considerable emphasis has been given to the understanding of normal exercise performance as well as to interpretation of pathophysiological abnormalities.

The clinical importance of exercise testing is obvious. Many patients, who are comfortable at rest, are unable to perform adequate exercise. It is important not to overlook the motivational component of exercise in these considerations; what represents a satisfactory activity level in one patient may be unsuitable for another. Clinical exercise testing arose because of the need to document objectively the exercise performance of patients for diagnostic, social, and; occasionally; legal reasons and to aid in detecting clinical abnormalities that are not evident from measurements of physiological performance made at rest. Prior to the advent of the microprocessor, evaluation of exercise performance was limited by the cumbersome technology. Under the best of conditions three, or at the most, five series of measurements could be made. Data processing

required days of calculation and chemical analysis of expired gas samples. The computer revolution has added greatly to the amount of data that can be assembled and evaluated for a single patient, and it probably is reasonable to state that more data is processed during a 10 minute breath-by-breath exercise test in a single patient than the sum of data for all of the non-computer assisted steady-state tests that ever have been performed. Standard, modular exercise units having the capabilities of what formerly constituted an entire laboratory are available currently. The expansion of clinical exercise testing into the assessment of cardiac failure, occult skeletal muscle abnormalities, non-invasive assessment of left ventricular dysfunction, and efficacy of treatment regimens for pulmonary hypertension is only the beginning of the expanded application of clinical exercise testing. The clinician evaluating such patients must not only understand the current technology of his/her subspeciality but also the technology of the related subspecialities.

The chapters written for this book fall into three basic categories. First, there are several chapters on the basics of gas exchange, bioenergetics and metabolism. These are included as the absolute essentials of basic science necessary to understand exercise performance. Second, several chapters are included that develop an understanding of the normal cardiac, musculoskeletal, pulmonary, and psychological components of exercise. The remaining chapters address the application of clinical exercise testing to assess specific pathophysiological abnormalities. These include some new techniques, which may not be available to all clinicians currently, but are likely to constitute the technology of the near future.

Alan Leff
Chicago

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Contributors

Louis Cohen, M.D.,
Professor of Medicine, Section of Cardiology, Division of the Biological Sciences, The University of Chicago
Joan Falk, Ph.D.
Clinical Psychologist, Department of Psychiatry, Division of Biological Sciences, The University of Chicago
James E. Hansen, M.D.
Professor of Medicine, Respiratory Physiology and Medical Division, Harbor/UCLA Medical Center, University of California, Los Angeles
Cynthia Kremser, M.D.
Clinical Instructor in Medicine, Department of Medicine, Division of the Biological Sciences, The University of Chicago
Alan R. Leff, M.D., Editor
Associate Professor, Section of Pulmonary and Critical Care Medicine and Committee on Clinical Pharmacology, Director, Pulmonary Medicine Service and Pulmonary Function and Exercise Physiology Laboratories, Division of the Biological Sciences, The University of Chicago
Julie Morgan, Ph.D.
Research Associate (Associate Professor), Section of Cardiology, Department of Medicine, Division of the Biological Sciences, The University of Chicago
John Nemanich, M.D.
Section of Cardiology, Division of the Biological Sciences, The University of Chicago

Randolph E. Patterson, M.D.
Associate Professor of Medicine, Director of Nuclear Cardiology, Carlyle Fraser Heart Center of Emory University at Crawford W. Long Memorial Hospital, Cardiology Division, Department of Medicine
Harold I. Palevsky, M.D.
Assistant Professor of Medicine, Cardiovascular-Pulmonary Division, University of Pennsylvania School of Medicine and Coordinator, Exercise Laboratory, Pulmonary Diagnostic Services, Hospital of the University of Pennsylvania
Sol I. Rajfer, M.D.
Assistant Professor of Medicine, Section of Cardiology and Committee on Clinical Pharmacology, Division of the Biological Sciences, The University of Chicago
Paul T. Schumacker, Ph.D.
Research Associate (Assistant Professor), Section of Pulmonary and Critical Care Medicine, Division of the Biological Sciences, The University of Chicago
Susan A. Ward, D. Phil.
Associate Professor of Anesthesiology, Department of Anesthesiology, University of California, Los Angeles; School of Medicine
Brian J. Whipp, Ph.D., D.Sc.
Professor of Medicine and Physiology, Division of Respiratory Physiology and Medicine, Harbor-UCLA Medical Center, University of California Los Angeles

CONTENTS

Brian J. Whipp

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Exercise Bioenergetics and Gas Exchange

The chief concerns of those interested in exercise testing—whether with regard to competitive athletic performance or to a patient with cardiovascular or pulmonary disease engaged in a mild domiciliary routine—are those factors that constrain the tolerable duration of a particular work rate below that required for the successful completion of the task. Work requires an effective interaction between the body's systems of provision (ie, muscular, cardiovascular, and respiratory) and its systems of maintenance (ie, thermoregulatory, fluid balance, acid-base, endocrine, etc.). This is necessary to maintain the physicochemical environment of the fluid milieux of the muscle cells in a state compatible with continued energy transfer. The body's energy exchange cascade therefore should be considered from "mouth to mitochondria."

STRUCTURAL CONSIDERATIONS

Muscle is best considered as an ensemble of noninteracting force-generating units, which are comprised of different fiber types. A single motor nerve to skeletal muscle typically innervates fewer than 10 fibers for muscles involved with fine movement (eg, the eye muscles) to more than 2000 for muscles of more coarse movement (eg, the soleus). The nerve-muscle fiber unit constitutes a "motor unit." The individual fibers of a motor unit, however, are not spatially contiguous, but rather are

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Table 1-1
Skeletal Muscle Fiber Classification

Characteristics	Type I Slow Oxidative	Type IIA Fast Oxidative	Type IIB Fast Glycolytic
"Color"	Red	Red	White
Myoglobin content	High	High	Low
Triglyceride content	High	Moderate	Low
Glycogen content	No appreciable differences		
Glycolytic capacity	Moderate	High	High
Oxidative potential (mitochondrial content, oxidative enzyme potential, capillary density)	High	High	Low
Fiber diameter	Moderate	Small	Large
Contractile behavior (time to peak tension following activation, myosin ATPase rate)	Slow	Fast	Fast

distributed throughout the muscle. Despite this spatial separation, each muscle fiber within a motor unit has been demonstrated to be of the same type.

The two most popular ways of characterizing the fiber types within a muscle are based on mechanical behavior and, in particular, the time taken to attain peak tension following activation; and histochemical make-up. And, as shown in Table 1-1, the Type I (or "slow-twitch") fiber has a relatively slow time to peak tension. This is presumed to result from the genetic control of the synthesis of myosin, which results in two isoenzymatic forms. In the Type I fibers, the myosin-ATPase dictates a relatively slow time to peak tension. However, the histochemical make-up of the Type I fiber confers a high oxidative potential as a result of its high mitochondrial content, its high concentrations of oxidative enzymes, its capillary density, and also the presence of myoglobin, which largely is responsible for the classification of the Type I fiber as "Red." (Myoglobin also is thought to provide facilitated diffusion of O_2 through the muscle tissue.)

The Type II (or "fast-twitch") fiber, on the other hand, has a relatively fast time to peak tension as a result of its different myosin ATPase (Table 1-1). However, it possesses a relatively low potential for oxidative metabolism; its mitochrondrial density and the concentrations of mitochrondrial enzymes are relatively low compared with the Type I fiber. There also are important differences in the glycolytic capacity of the Type I and II fibers; the Type I fiber is capable of utilizing glycogen at a considerably lower rate than the faster Type II fiber. The Type I fiber may

be considered to be "designed" for oxidative metabolism, whereas the Type II fiber tends towards rapid glycolytic, and hence lactate-producing, energy exchange.

It should be emphasized that muscle-fiber typing is much more complex than has been described here. For example, the Type II fibers usually are classified as either Type IIA or IIB (Table 1-1), reflecting differences both in fiber diameter and oxidative capacity. However, it is beyond the scope of this text to discuss the issue in greater depth, and the interested reader is referred to any of several excellent reviews on this topic[1,2] (see also Chapter 9).

The purpose of this characterization of skeletal muscle fiber types is to indicate that the consequences of performing a given work rate depend in part upon the pattern of fiber-type recruitment for the force generation. The sequence of recruitment of motor units is such that the smallest motor units are recruited first (these being Type I, slow-twitch, high-oxidative fibers); exercise requiring relatively low rates of power development results in utilization of highly oxidative units. However, with rapid generation of power, the Type II (fast-twitch) units are recruited. These are the high-glycolytic, low-oxidative type; rapid depletion of glycogen ensues together with its consequent high lactate yield. Slow-twitch fibers typically are innervated by relatively small motoneurones that have relatively low excitation thresholds, whereas the fast-twitch fibers tend to be innervated by larger motoneurones with high thresholds for excitation. This gradation of motoneurone recruitment, as a function of the relative size of the motoneurones, is termed the "size principle" of recruitment.[3]

SUBSTRATE UTILIZATION

Skeletal muscle may be considered to be a machine that transforms the chemical energy of ingested food into the mechanical energy of muscular contraction and work. The substrate free energy, however, may not be used directly by the contractile mechanism to fuel these reactions. Rather, adenosine triphosphate (ATP), the terminal phosphate bond of which has a high free energy of hydrolysis, serves as the obligatory intermediary. Because of the high free energy of hydrolysis, ATP is commonly referred to as a "high-energy" phosphate. Cleavage of the terminal phosphate bond of ATP yields sufficient free energy (values of up to 12–14 Kcal having been estimated under physiologic conditions) for the "make-and-break" reactions between the actin and myosin crossbridges that are thought to be the basis for force generation in muscle.

ATP may be generated from carbohydrate, fat, or protein, although

Table 1-2
Caloric Equivalents of Substrate Oxidation and Gas Exchange

Substrate	RQ*	Kcal/g	Kcal/L O_2	Kcal/L CO_2	Liters O_2/g	Liters CO_2/g
Carbohydrate	1.00	4.1	5.05	5.05	0.81	0.81
Fat	0.71	9.3	4.74	6.67	1.96	1.39
Protein	0.81	4.2	4.46	4.57	0.94	0.75

* RQ is the respiratory quotient.

protein generally is considered to subserve an insignificant role as a substrate during exercise. Consequently, the proportional contribution of carbohydrate and fat as fuels for exercise can be determined from steady-state gas exchange measurements at the mouth. In the steady state, the ratio of CO_2 produced to O_2 consumed is termed the respiratory quotient (RQ), the value of which varies with the substrate mixture being catabolized (Table 1-2); carbohydrate has an RQ of 1.0 and fat a value close to 0.7 (but with small differences depending upon the particular fatty acid being oxidized). ATP can be formed in the working muscle from the breakdown of carbohydrate from sources such as muscle glycogen and blood glucose (the latter deriving from hepatic glycogen stores) and from the catabolism of fat from both intramuscular and extramuscular storage sites.

For moderate intensity exercise, which relies solely on aerobic metabolism, a mixture of fat and carbohydrate typically is catabolized. Oxygen is utilized, and CO_2 and water are the end products:

Carbohydrate (eg, glucose): $C_6H_{12}O_6 + \underbrace{6O_2 \rightarrow 6CO_2}_{RQ = 1.0} + 6\,H_2O + 36ATP$ **I**

$\underbrace{\qquad\qquad\qquad\qquad}_{\sim P:O_2 = 6.0}$

Fatty acids (eg, palmitic acid): $C_{16}H_{32}O_2 + \underbrace{23O_2 \rightarrow 16CO_2}_{RQ = 0.71} + 16H_2O + 130ATP$ **II**

$\underbrace{\qquad\qquad\qquad\qquad}_{\sim P:O_2 = 5.65}$

From an energetic standpoint, carbohydrates and fatty acids are equally efficient at providing energy for the work of muscular contraction,[4] both substrates converting similar fractions of their substrate free energy into the bond energy of ATP (ie, 18 Kcal/ATP molecule).

However, fatty acids have a significant advantage as a fuel in terms of available energy yield/gram (Table 1-2). In addition, the amount of fat stored in the body (chiefly as adipose tissue) is much larger than that of carbohydrate; a "standard" 70 kg man with a 15 percent fat content, for example, would have a potential energy store for fat of some 100,000 Kcal, whereas the carbohydrate store would be only about 2000 Kcal.

But while fat is the dominant storage fuel, carbohydrate is a more efficient fuel for oxidative energy yield, providing some 7 percent more energy/liter of O_2 than fat (Table 1-2). Furthermore, carbohydrate oxidation results in approximately 24 percent more CO_2 production/Kcal of energy yield than does that of fat (Table 1-2). This has important consequences, for example, in situations where a patient's work tolerance is limited largely by his or her ability to generate a level of ventilation adequate to "clear" the metabolically-produced CO_2 load and, therefore, to preserve arterial P_{CO_2} and pH within normal limits. Such an individual would benefit from catabolizing fatty acids rather than carbohydrates because of the lower CO_2 production, although the cost would be a small obligatory reduction in PO_2.

The major intramuscular carbohydrate store is in the form of glycogen. This accounts for a total of 300–400 grams. The available glycogen is limited to that stored in those muscles that are generating force for the work, and there is little or no glycogen utilization in the noncontracting units.[5] The glycogen content in muscle can be altered by manipulations such as a combination of diet and exercise. For example, if intense exercise is used to deplete muscle glycogen stores and then a carbohydrate-rich diet is ingested, the glycogen content of the "exercised" muscle can be increased markedly.

There is approximately 20 mg triglyceride/g of skeletal muscle (wet weight). This source recently has been shown to account for approximately 75 percent of the total energy derived from lipid during sustained exercise at about 50 percent of maximal exercise ($\dot{V}O_{2max}$).[6] Consequently, fatty acid oxidation from adipose tissue accounts for only 25 percent of the total derived energy. Furthermore, intramuscular triglyceride also has been shown to be the dominant lipid substrate during short-term intermittent exercise.

The extramuscular fat source is comprised of both free fatty acids and the adipose tissue. The plasma free fatty acid levels are relatively low at rest (about 0.5 mEq/L) and also during moderate exercise (about 2 mEq/L); the turnover rate is high, however. These play an important energetic role during prolonged exercise. Thus, fatty acids are mobilized from different regions of the body by catecholamine-mediated lipolysis, as needed, to maintain or increase plasma fatty acid levels throughout the exercise. This results both from direct sympathetic innervation of adipose

tissue (norepinephrine) and from blood-borne catecholamines released from the adrenal medulla.

The formation of ATP in the working muscle also can be sustained by anaerobic means within the cytoplasm under conditions in which the O_2 availability to the working muscle is impaired or when O_2 is available but not utilized (as, for example, in the case of a muscle fiber having relatively few mitochondria, a relatively low oxidative enzyme capacity, or both).

Under anaerobic conditions, carbohydrate is the obligatory substrate for metabolism and results in the generation of lactic acid as an additional end product (Fig. 1-1). The ATP yield is substantially lower, however, than for the complete oxidation of carbohydrate, ie, only 2 ATP molecules per glucosyl unit (Fig. 1-1):

$$C_6H_{12}O_6 \rightarrow 2C_3H_6O_3 + 2\ ATP \qquad \textbf{III}$$

Thus, to produce ATP anaerobically from carbohydrate at the same rate as under aerobic conditions, the rate of glucose utilization must increase approximately 19-fold for those units producing the lactate.

The lactic acid that is formed anaerobically in the muscle cells is dissociated almost completely at the pH of body fluids, being buffered predominantly by the carbonic acid-bicarbonate system:

$$\underset{\text{(lactic acid)}}{CH_3 \cdot CHOH \cdot COO^-} + H^+ + \underset{\left(\begin{smallmatrix}\text{sodium}\\ \text{bicarbonate}\end{smallmatrix}\right)}{NaHCO_3} \rightarrow \qquad \textbf{IV}$$

$$\underset{\left(\begin{smallmatrix}\text{sodium}\\ \text{lactate}\end{smallmatrix}\right)}{CH_3 \cdot CHOH \cdot COONa} + \underset{\left(\begin{smallmatrix}\text{carbonic}\\ \text{acid}\end{smallmatrix}\right)}{H_2CO_3}$$

In the presence of the available enzyme carbonic anhydrase, the carbonic acid rapidly dissociates to form water and carbon dioxide:

$$H_2CO_3 \rightarrow H_2O + CO_2 \qquad \textbf{V}$$

It should be emphasized that this carbon dioxide is formed from buffering reactions and not from metabolic reactions within the mitochondria.

Muscle glycogen is an especially important fuel for prolonged, heavy exercise, which relies upon anaerobic metabolism for energy production.[7] Thus, during exercise at an intensity of about 70 to 80 percent of $\dot{V}O_{2max}$, muscle glycogen levels fall. This glycogen depletion in the force-generating units is considered to limit the exercise.

Although an additional 10 grams or so of glucose is available in the blood and interstitial fluid, the largest extramuscular carbohydrate store is the liver, accounting for some 50–90 grams. This, however, is a very labile

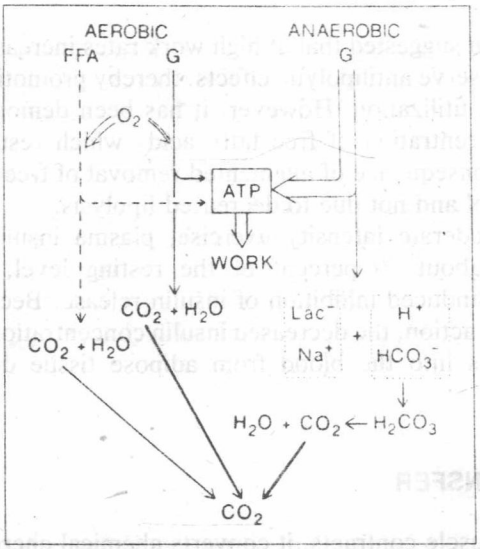

Fig. 1-1. Schematic representation of aerobic and anaerobic pathways of substrate utilization in working muscle, where G and FFA are available pools of glucose and glycosyl units and of free fatty acids, respectively. Thickness of arrows of the reaction routes (substrate utilization, O_2 consumption, CO_2 production) is proportional to corresponding rates of material flux (substrate, O_2, CO_2) per unit of ATP production. [Reproduced from Ward SA, Davis JA, Whipp BJ: The physiologic basis of exercise testing: principles. J Cardiovas Pulmonary Tech 10:23–30, 1982, with permission].

store and is affected by both diet and exercise. For example, one day of a carbohydrate-free diet will virtually deplete the liver glycogen stores, whereas this can be doubled by a day on a carbohydrate-rich diet. The liver glycogen stores also are reduced during prolonged exercise to maintain normal levels of blood glucose. This release from the liver during exercise is influenced by the blood glucose level and by the circulating levels of hormones such as insulin, glucagon, epinephrine, and norepinephrine.

This allows blood glucose levels to be maintained during exercise until muscle and liver glycogen contents fall to low levels. At this stage, the blood glucose concentration also starts to fall, although it normally does not fall to levels sufficiently low to evoke central nervous system symptoms of hypoglycemia.