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Purpose

Introduction

The human body is designed for the performance of exercise. Habitual patterns of exercise activity are known to be linked to health, well-being, and risk of disease. In fitness and athletics, exercise capacity is linked to performance and achievement. In clinical medicine, exercise performance is intricately related to functional capacity and quality of life. Hence the importance of exercise testing and interpretation as a means of determining exercise capacity and identifying factors which might limit exercise performance. Exercise professionals, whether concerned with physical fitness and sports or clinical medicine and rehabilitation, should be well versed in methods of exercise testing and interpretation. Hence the need for a practical guide to assist in this undertaking.

A wide variety of methods have evolved for the purpose of assessing exercise capacity and identifying specific limiting factors. Field tests are commonly used in fitness and sports to assess athletic performance, but can be used to assess progress in clinical or rehabilitative settings. Laboratory exercise protocols are also used to assess fitness and are often combined with electrocardiography to diagnose coronary artery disease. Symptom-limited, incremental exercise testing, including measurement of ventilation and gas exchange, has proven to be an important diagnostic, clinical, prescriptive, and rehabilitative tool. These more complex laboratory tests evaluate the integrated human cardiovascular, ventilatory, and musculoskeletal responses to exercise. Whether the assessment is conducted in the field or in the laboratory, all of these exercise tests require careful attention to detail if meaningful information is to be derived.

This book provides a detailed examination of the instruments, methods, proper conduct, and interpretation of a variety of exercise tests. This is meant to be a practical guide, assisting the reader in every step of the process with fundamental information, examples, and practice using a time-tested methodology. The next section of this chapter reviews the basic exercise physiology that underlies exercise testing and interpretation. It is included not as a primer, but rather to illustrate the important concepts involved.

Basic exercise physiology

Coupling of cellular respiration to external work

During the performance of most types of exercise, it is well known that oxygen uptake ($\dot{V}O_2$) is tightly coupled to external work rate ($\dot{W}$) or power output. The essential components of this coupling are illustrated in Figure 1.1. Central to our understanding of exercise physiology is the measurement of alveolar oxygen uptake ($\dot{V}O_{2alv}$) by collection and analysis of exhaled gases. $\dot{V}O_{2alv}$ provides the systemic arterial oxygen content for delivery to exercising muscles. Hence, the extent to which $\dot{V}O_{2alv}$ matches muscle oxygen consumption ($\dot{Q}O_{2mus}$) is in part a reflection of the effectiveness of oxygen delivery via the

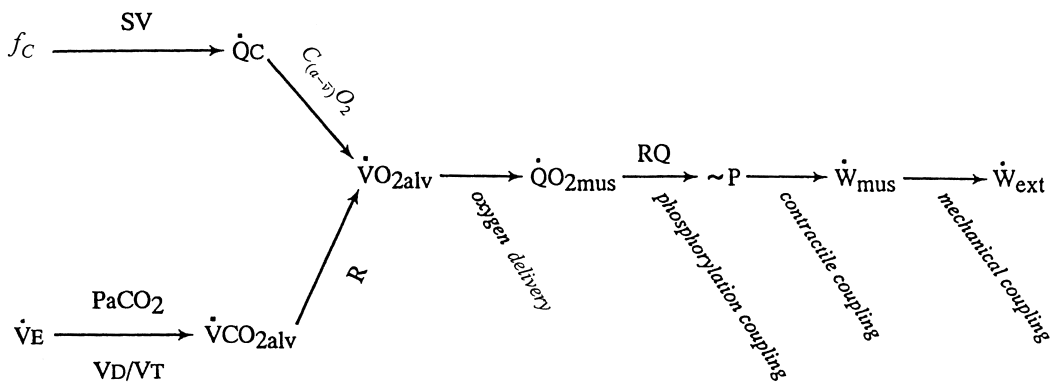

Figure 1.1 Cardiovascular and ventilatory coupling to external work. See the accompanying text and Appendix A for definitions of the symbols.

circulation. In steady-state conditions $\dot{V}o_{2alv}$ should reflect the oxygen consumption of all tissues, including $\dot{Q}o_{2mus}$. However, in unsteady-state conditions, such as during an incremental exercise test or during the transition from rest to constant work rate exercise, changes in $\dot{V}o_{2alv}$ typically lag behind changes in $\dot{Q}o_{2mus}$. In exercising muscle oxygen is utilized in the production of high-energy phosphate compounds (~*P*). The yield of ~*P* per oxygen molecule is dependent on the substrate being utilized for energy generation, which in turn dictates the respiratory quotient (RQ) of the muscle tissue. The conversion of chemical energy in the form of ~*P* to intrinsic muscle work ($\dot{W}_{mus}$) depends on contractile coupling and mechanisms that result in actin–myosin cross-bridge formation and muscle shortening. Finally comes the conversion of $\dot{W}_{mus}$ to external work ($\dot{W}_{ext}$), which can be measured by an ergometer. This last stage has a significant effect on work efficiency, being influenced by musculoskeletal coordination and undoubtedly incorporating a skill factor. Aside from the choice of substrate and the skill factor, it can be appreciated that the sequence of mechanisms described above is largely defined by immutable metabolic reactions and ultrastructural properties of human skeletal muscle. Not surprisingly, therefore, when a short-duration exercise protocol which utilizes carbohydrate as the predominant metabolic substrate is performed on a cycle ergometer which minimizes the skill factor, the relationship between $\dot{V}o_{2alv}$ and $\dot{W}_{ext}$ demonstrates linearity and remarkable consistency among normal subjects (see Chapter 4).

Cardiopulmonary coupling to external work

Integrated exercise testing usually attempts to study the simultaneous responses of the cardiovascular and pulmonary systems. Commonly the cardiovascular response is judged by changes in heart rate (f_C) with respect to measured $\dot{V}o_2$ whereas the pulmonary response is judged in terms of minute ventilation ($\dot{V}_E$). Figure 1.1 illustrates how each of these variables is coupled to $\dot{V}o_2$.

Cardiac output ($\dot{Q}_C$) is of central importance in the cardiovascular coupling. The Fick equation (see Chapter 4) reminds us that the relationship between $\dot{Q}_C$ and $\dot{V}o_2$ is determined by the difference in oxygen content between systemic arterial blood and mixed systemic venous blood ($C_{(a-\bar{v})}O_2$). Obviously $\dot{Q}_C$ and f_C are linked through cardiac stroke volume (SV).

Carbon dioxide output ($\dot{V}co_2$) is of central importance in ventilatory coupling. The Bohr equation (see Chapter 4) reminds us that the relationship between $\dot{V}co_2$ and $\dot{V}_E$ is determined by the level at which arterial carbon dioxide tension ($Paco_2$) is regulated and the ratio of dead space to tidal volume (V_D/V_T). Obviously alveolar $\dot{V}co_2$ and $\dot{V}o_2$ are linked by the respiratory exchange ratio, *R*.

Metabolic pathways

This book will not attempt a detailed description of all of the metabolic pathways involved in exercise. However, a simplified description of cellular energy generation follows and is illustrated in Figures 1.2 and 1.3.

Whilst fat and protein degradation can sometimes be important in the metabolic response to exercise, undoubtedly the principal substrate for muscle metabolism is carbohydrate in the form of muscle glycogen. The degradation of glycogen to pyruvate occurs in the cytosol and is termed anaerobic glycolysis or the Embden–Meyerhof pathway (Figure 1.2). Firstly, glycogen must be split into glucose units by a glycogen phosphorylase. Each molecule of glucose is then converted to two molecules of pyruvate, with the net generation of two ATP molecules and four hydrogen ions. The hydrogen ions are taken up by the coenzyme NAD to form $NADH + H^+$.

Pyruvate undergoes oxidative decarboxylation that irreversibly removes carbon dioxide and attaches the remainder of the pyruvate molecule to coenzyme A (CoA), forming acetyl-CoA. Note that acetyl-CoA is also the product of fatty acid β-oxidation. Acetyl-CoA enters the mitochondrion and combines with oxaloacetate to become citrate. In this way acetyl-CoA becomes fuel for the tricarboxylic acid (TCA) cycle, otherwise known as the Krebs cycle or citric acid cycle (Figure 1.2). This sequence of enzymatic reactions dismembers acetyl-CoA, yielding carbon dioxide and hydrogen atoms. Once again the hydrogen ions are accepted by coenzymes. For every acetyl unit consumed in the cycle, there are two carbon dioxide molecules produced along with three $NADH + H^+$ and one $FADH_2$. In addition there is one directly produced molecule of GTP which contains an equivalent amount of energy to ATP. Note that by accepting hydrogen ions the coenzymes NAD and FAD play a vital role in trapping energy.

The main engine for cellular energy generation is the mitochondrial pathway for oxidative phosphorylation, which is shown in Figure 1.3. This pathway is also called the respiratory chain or electron transport chain. The chain is a complex device consisting of lipoproteins with different cytochromes, metals, and other cofactors. Essentially, the chain facilitates the flow of electrons from coenzymes $NADH + H^+$ and $FADH_2$ releasing energy for the phosphorylation of ADP to ATP at three sites. Finally, two electrons are combined with two protons (H^+) and oxygen to form water. $NADH + H^+$ enters the first stage of the chain, giving rise to NAD and three ATP, whereas $FADH_2$ enters the second stage of the chain, giving rise to FAD and two ATP. The oxidized coenzymes are released and become available to catalyze dehydrogenase reactions further.

Summarizing all of the pathways described above, the usual process of cellular energy generation can be described by two equations:

$$NADH + H^+ + \tfrac{1}{2}O_2 + 3Pi + 3ADP \rightarrow 3ATP + NAD + H_2O \quad (1.1)$$

$$FADH_2 + \tfrac{1}{2}O_2 + 2Pi + 2ADP \rightarrow 2ATP + NAD + H_2O \quad (1.2)$$

Complete combustion of one molecule of glucose in the presence of sufficient oxygen leads to the generation of approximately 36 molecules of ATP. This number varies depending on how one views the degradation of glycogen and to what extent energy is consumed transporting protons from anaerobic glycolysis into the mitochondrion. $NADH + H^+$ does not cross the mitochondrial membrane and therefore its protons are transferred by a ''shuttle'' to FAD which enters the electron transport chain at the second rather than the first stage.

When oxygen is not available in sufficient quantity for complete oxidative phosphorylation, then several important changes ensue:

1. The mitochondrial pathways, including the TCA cycle and electron transport chain, are ineffective.
2. Pyruvate accumulates in the cytosol and is converted to lactate.
3. The regeneration of ATP from ADP slows by a factor of approximately 18.
4. Muscle glycogen is more rapidly consumed.

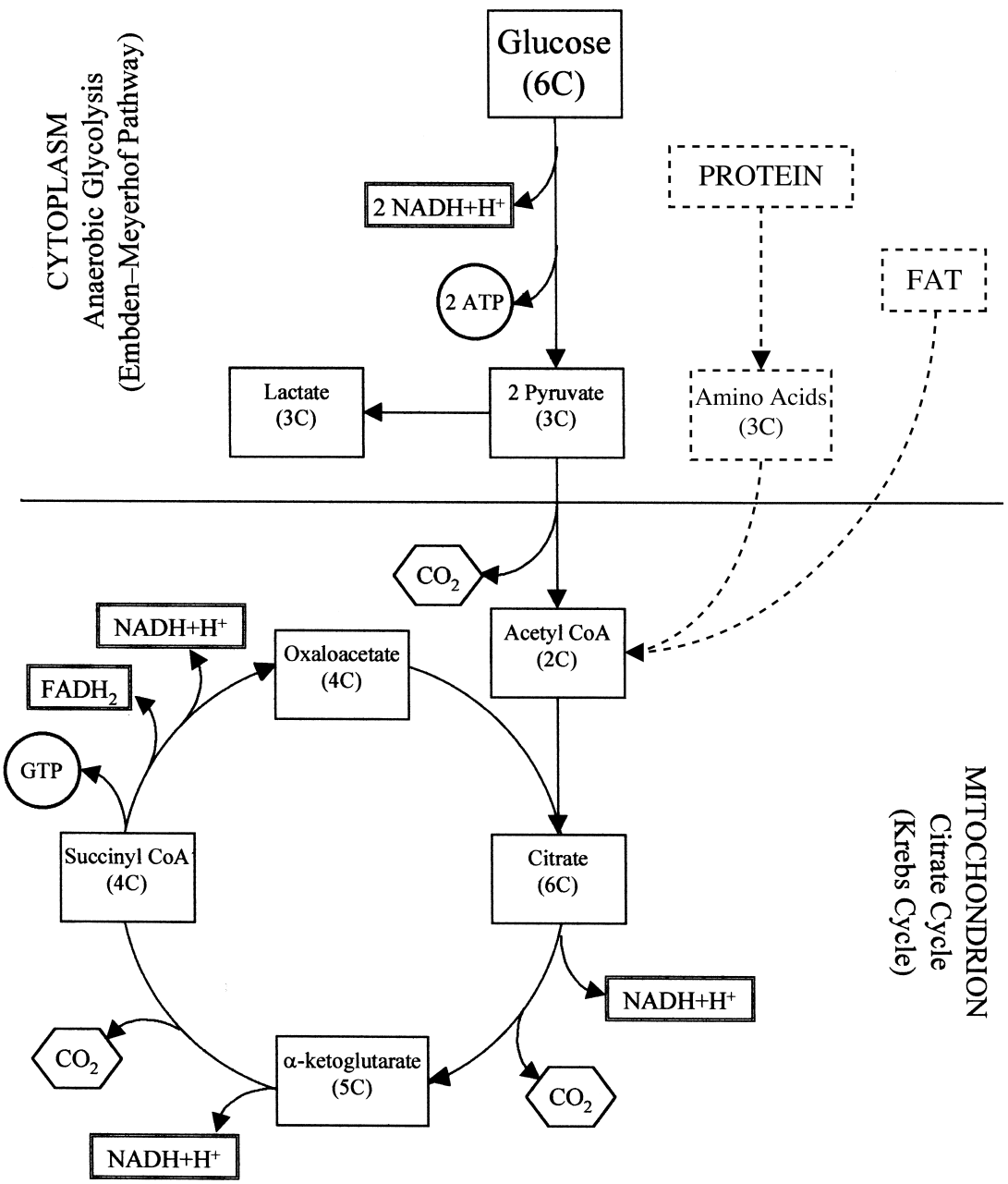

Figure 1.2 Metabolic pathways for cellular energy generation showing anaerobic glycolysis in the cytoplasm and the citrate cycle in the mitochondrion.

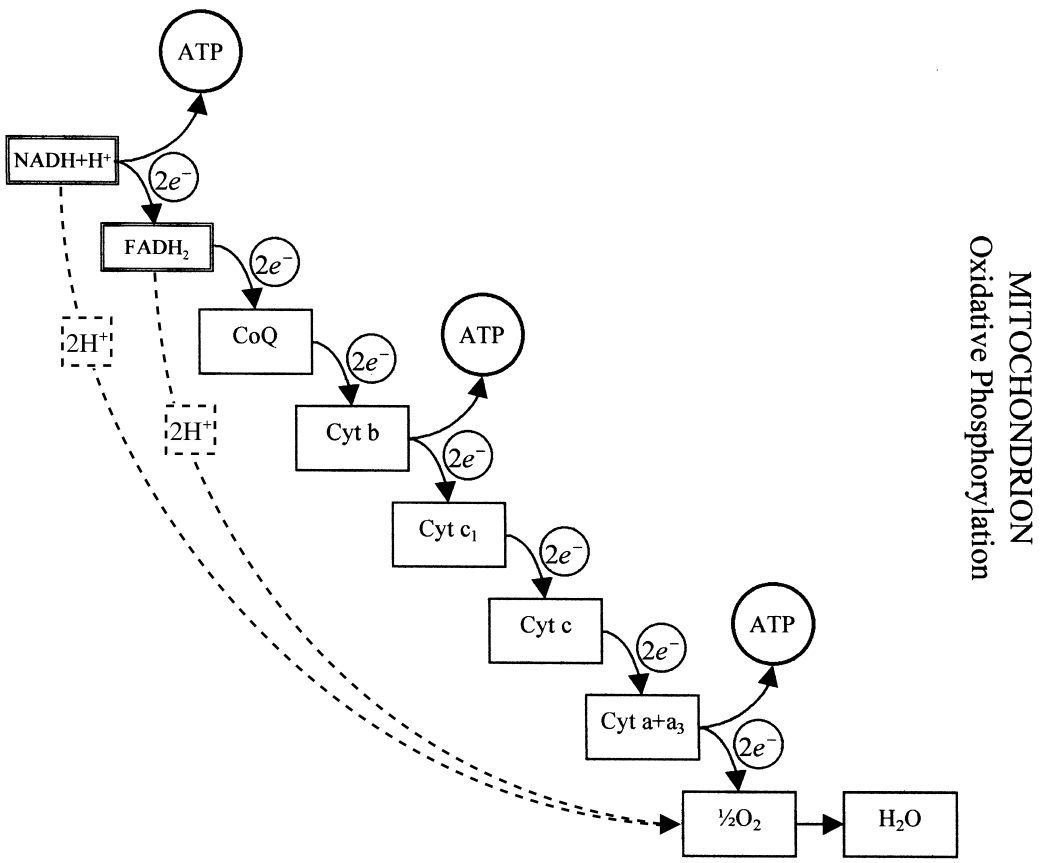

Figure 1.3 Schematic representation of the mitochondrial electron transport chain.

5. Lactate effluxes into the plasma where bicarbonate buffering generates carbon dioxide.
6. Gas exchange and ventilatory changes occur in response to the need to eliminate the additional carbon dioxide.

A compromised ability to regenerate ATP from ADP by oxidative phosphorylation leads to the accumulation of ADP. In these circumstances the myokinase reaction can combine two ADP molecules to create one ATP molecule and one AMP molecule (see Equation 1.3). AMP is then degraded by the action of the enzyme myoadenylate deaminase to create inosine and ammonia (see Equation 1.4).

$$2\text{ADP} \rightarrow \text{ATP} + \text{AMP} \quad (1.3)$$

$$\text{AMP} \rightarrow \text{Inosine} + \text{NH}_3 \quad (1.4)$$

These secondary pathways of ATP regeneration seem to be invoked in various clinical conditions which result in cellular energy deprivation.

Aerobic and anaerobic metabolism

Considerable controversy surrounds the use of the terms aerobic and anaerobic to describe the physiological responses to exercise because of the temptation to associate anaerobic metabolism simplistically with insufficient oxygen uptake by the body. During incremental exercise there is not a sudden switch from aerobic metabolism to anaerobic

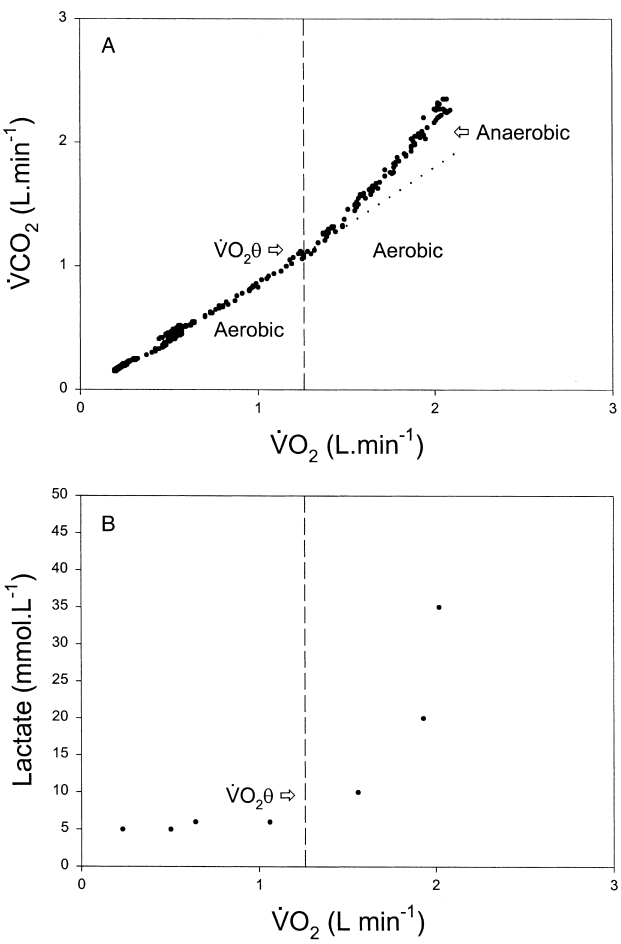

Figure 1.4 Physiological domains of exercise showing the contribution of aerobic and anaerobic metabolism to gas exchange. (A) Changes in $\dot{V}CO_2$ with increasing $\dot{V}O_2$. (B) Corresponding increase in blood lactate. $\dot{V}O_2\theta$ is the metabolic threshold separating the aerobic from the aerobic plus anaerobic domains.

metabolism when the supply of oxygen runs short. Nevertheless, it is possible to distinguish two different domains of exercise intensity.

Lower-intensity exercise predominantly utilizes aerobic metabolic pathways, including oxidative phosphorylation for the regeneration of ATP. A small amount of lactate is formed in exercising muscle but blood lactate levels remain low and stable due to effective lactate disposal in other tissues. Constant work rate exercise of this intensity can be performed for long periods without fatigue and the physiological parameters of the exercise response exhibit a steady state.

By contrast, higher-intensity exercise utilizes a combination of aerobic and anaerobic metabolism in order to produce sufficient quantities of ATP. A sustained increase in blood lactate occurs, resulting in a measurable increase in carbon dioxide output derived from bicarbonate buffering, as illustrated in Figure 1.4. In other words, the physiological parameters of the exercise response do not achieve a steady state. A distinction between these two physiological domains of exercise intensity can often be made using noninvasive gas exchange measurements.

In summary, two domains of exercise intensity can be identified and, for the purposes of exercise testing and interpretation, it is helpful to consider the transition between these domains as a metabolic threshold. At the same time the terms aerobic and anaerobic should be used strictly to describe metabolic processes which respectively use oxygen or do not use oxygen regardless of its availability.

Threshold concepts

Incremental exercise testing in a variety of circumstances is likely to reveal not only limitations to maximal performance but also certain thresholds of exercise intensity below or above which different physiological or pathological factors influence the exercise response. Some of these thresholds might be clear-cut. Others will be represented by more gradual transitions. The preceding discussion indicates that the transition from an exercise domain where metabolism is predominantly aerobic to a domain where anaerobic metabolism plays an increasing role is not necessarily clear-cut. However, for the purposes of exercise test interpretation, definition of this threshold has practical value. This is true for exercise tests that assess physical performance in apparently healthy subjects as well as tests which attempt to define exercise limitations in pa-

Table 1.1. Energetic properties of different metabolic substrates relevant to the exercise response

Substrate	Respiratory quotient	Efficiency of energy storage (kcal · g^{-1})	Caloric equivalent for oxygen (kcal · l^{-1})	Caloric eqivalent for carbon dioxide (kcal · l^{-1})
Carbohydrate	1.00	4.1	5.05	5.05
Fat (e.g., palmitate)	0.71	9.3	4.74	6.67
Protein	0.81	4.2	4.46	4.57

tients with illness. Other clinical thresholds of practical importance in patients with cardiovascular or pulmonary diseases undergoing exercise rehabilitation are described below in the section on exercise prescription.

Energetics and substrate utilization

This section on basic exercise physiology concludes with a brief consideration of cellular energetics and substrate utilization. Whatever the substrate being used for muscle metabolism during exercise, it is important to consider the related processes of cellular energy generation both in terms of their efficiency and also the gas exchange and ventilatory consequences for the exercise response. Firstly, let us consider the chemical equations that define the complete oxidation of carbohydrate (glucose) and a fat (palmitate) in the presence of sufficient oxygen, to carbon dioxide and water.

For glucose:

$$C_6H_{12}O_6 + 36ADP + 36Pi + 6O_2 \rightarrow 6CO_2 + 6H_2O + 36ATP \quad (1.5)$$

For palmitate:

$$C_{15}H_{31}COOH + 129ADP + 129Pi + 23O_2 \rightarrow 16CO_2 + 16H_2O + 129ATP \quad (1.6)$$

These equations enable calculations of the respiratory quotient (RQ, or $\dot{V}co_2$ divided by $\dot{V}o_2$), the efficiency of energy storage, and the caloric equivalents for oxygen and carbon dioxide of each metabolic substrate, as shown in Table 1.1. The corresponding values for protein are also included.

These different respiratory quotients are well known. Table 1.1 shows that fat is almost twice as efficient as a storage medium for energy as compared with both carbohydrate and protein. The caloric equivalents for oxygen indicate that carbohydrate is the most efficient substrate in terms of energy generation for every liter of oxygen used in its combustion. Work efficiency during an incremental exercise test, as illustrated by the relationship between external work rate ($\dot{W}$) and $\dot{V}o_2$ is clearly related to the caloric equivalent for oxygen of the substrate or substrates being metabolized during the study. Finally, the caloric equivalents for carbon dioxide serve as a reminder that fat generates less carbon dioxide than carbohydrate and should therefore demand a smaller ventilatory response.

Exercise test nomenclature

Many terms have been used to describe exercise tests leading to some confusion with the nomenclature. However, exercise testing can be conveniently partitioned into two general disciplines, two principal settings and numerous specific protocols (Figure 1.5). The discipline, setting, and protocol of the exercise test should be appropriate for the purpose of the test with the intention of deriving the desired information with the greatest ease and fidelity. The two general exercise test disciplines are performance exercise testing (PXT) and clinical exercise testing (CXT). A PXT is usually performed on apparently healthy individuals for the purposes of quantification of aerobic capacity or fitness assessment, exercise prescription, and response to training or

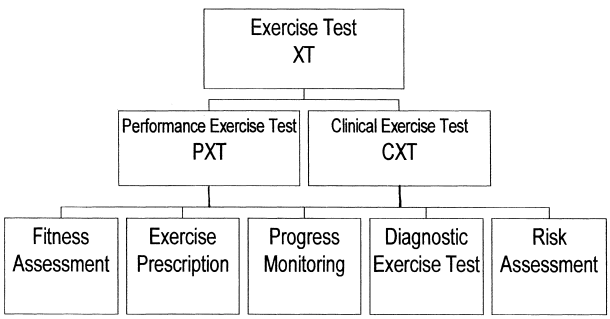

Figure 1.5 A classification for exercise testing distinguishing performance exercise tests for healthy individuals from clinical exercise tests used for the evaluation and management of patients.

lifestyle modification. A CXT is performed on subjects presenting with symptoms and signs of disease for the purposes of diagnosis, risk assessment, progress monitoring, and response to therapeutic interventions. The setting for both PXT and CXT can be in the field or in the laboratory. The convention displayed in Figure 1.5 will be used throughout this book. Chapter 3 describes detailed methods for a variety of field and laboratory exercise tests within these categories.

Evaluation of the exercise response

An exercise response might be judged normal or abnormal on the basis of one or more specific variables or based on a range of variables, which together constitute a physiological response pattern. The extent of this analysis clearly depends on what type of exercise test has been performed, how much data is available, and what the normal response would be expected to resemble. A normal response can be identified in the context of a true maximal or submaximal effort. On the other hand, when abnormalities are identified they need to be characterized according to certain recognized abnormal exercise response patterns (Table 1.2).

A detailed analysis of abnormal exercise response patterns is illustrated in Chapter 5. Cardiovascular limitation is normal, but when it is associated with an abnormal cardiovascular response pattern or impaired oxygen delivery, this points to diseases of the heart or circulation, or perhaps the effects of medications. Ventilatory limitation is usually abnormal and points to diseases of the lungs or respiratory muscles. Occasionally, one sees failure of ventilation due to abnormal control of breathing. With more sophisticated types of exercise testing, abnormalities of pulmonary gas exchange can be identified. This type of abnormality generally points to diseases of the lungs or pulmonary circulation. Reduced aerobic capacity and impairments of the metabolic response to exercise can be due to abnormalities of muscle metabolism due to inherited or acquired muscle disease. Finally, abnormal symptom perception can be associated with malingering or psychological disturbances. Figure 1.6 summarizes the principal categories of exercise limitation and indicates how many common conditions and diseases impact cardiovascular and ventilatory coupling to external work.

Specific applications

Exercise testing has wide applications in health and disease. This section proffers several ways in which exercise testing may be employed, including assessment of physical fitness, evaluation of exercise intolerance, diagnosis of disease, exercise prescription both in sports and clinical rehabilitation, and evaluation of therapeutic interventions. These broad categories, along with more specific applications of exercise testing, are listed in Table 1.3.

Assessment of physical fitness

Aerobic performance is one of the essential elements of physical fitness, along with muscle strength, flexibility, and body composition. Aerobic performance is defined by certain parameters that can be measured using carefully selected exercise-testing protocols. The best known of these parameters is maximum oxygen uptake ($\dot{V}O_{2max}$). The

Table 1.2. Recognizable exercise response patterns which assist in exercise test interpretation

Normal response	Abnormal response
Maximal effort	Abnormal cardiovascular response pattern
Cardiovascular limitation	Impaired oxygen delivery
Suboptimal effort	Ventilatory limitation
	Abnormal ventilatory response pattern
	Abnormal ventilatory control
	Impaired gas exchange
	Abnormal muscle metabolism
	Abnormal symptom perception

other parameters are the metabolic threshold ($\dot{V}O_2\theta$), work efficiency (η), and the time constant for oxygen uptake kinetics ($\tau\dot{V}O_2$). Each of these parameters is described in detail in Chapter 4. They can be derived with accuracy provided the appropriate instrumentation and testing methods are used, as described in Chapters 2 and 3. Determination of one or more of the parameters of aerobic performance for a given individual facilitates the prescription of exercise based on meaningful physiological data. Furthermore, the identification of the important metabolic markers such as $\dot{V}O_{2max}$, $\dot{V}O_2\theta$ and the ventilatory threshold ($\dot{V}_E\theta$) defines the physiological domains of exercise intensity for a given individual. These domains can in turn be used to prescribe an exercise program logically based on knowledge of the metabolic profile of that individual.

Exercise testing, with repeated determination of certain parameters, e.g., timed walking distance, $\dot{V}O_{2max}$ (directly measured or estimated), the relationship between f_C and $\dot{W}$, and $\dot{V}O_2\theta$ can be used to track individual progression in response to exercise training or a program of rehabilitation. Properly conducted field tests using appropriate instruments (see Chapter 2) generally provide reliable results. Field tests are valuable for progress monitoring, even though absolute accuracy may be less than desired. This latter point is particularly applicable to estimations of $\dot{V}O_{2max}$.

Evaluation of exercise intolerance

In the clinical laboratory specially designed exercise-testing protocols can be used to study the wide range of physiological variables during incremental exercise. Applied to a symptom-limited maximal exercise test, this approach facilitates the identification of specific physiological limitations for a given individual. Hence, when an individual complains of exercise intolerance, the physiological responses can be carefully examined to see if they offer a plausible explanation for the subject's symptoms.

A special application in the evaluation of exercise intolerance is disability evaluation. A successful disability claim often has important financial implications for the claimant. Thus, it needs to be supported by objective measures of exercise incapacity. The symptom-limited incremental exercise test identifies those with genuine exercise limitation, those who deliberately give a submaximal effort, and those who have normal exercise capacity despite their symptoms.

Differential diagnosis of disease

Cardiovascular diseases

One of the most valuable applications of clinical exercise testing is the ability to distinguish cardiovascular from pulmonary causes of exercise limitation. In the arena of clinical exercise testing, particularly with older subjects, cardiovascular and pulmonary diseases frequently coexist. The symptom-limited incremental exercise test helps identify which of these conditions is the limiting factor. This can have important implications in terms of the direction and goals of treatment.

A variety of incremental treadmill protocols have been used for the detection of myocardial ischemia due to coronary artery disease. These protocols are usually limited to measurement of heart rate, blood pressure, and a detailed recording of the electrocardiogram. The incremental exercise test can also identify early cardiovascular disease such as cardiomyopathy. However, it is often difficult to distinguish early cardiovascular disease from physical

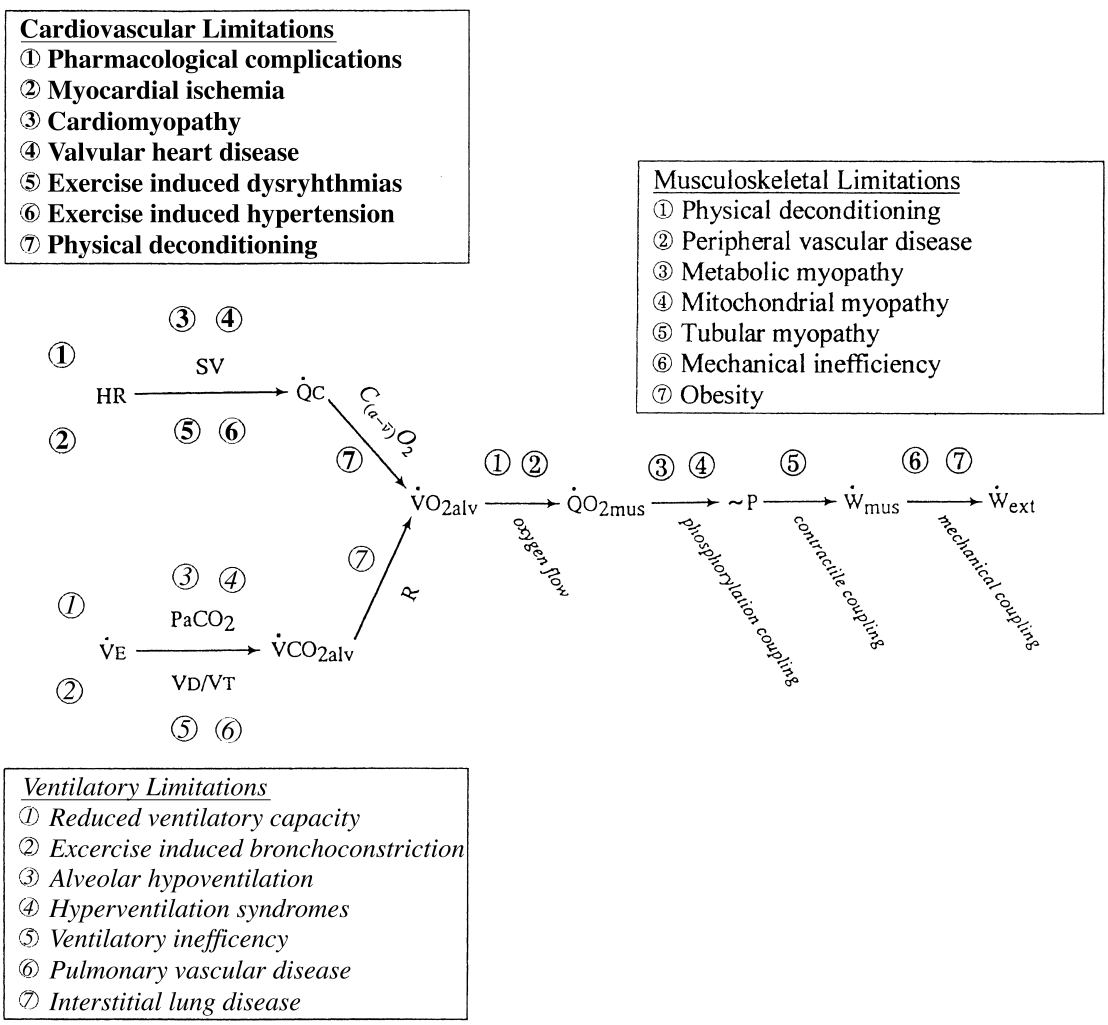

Figure 1.6 Cardiovascular, ventilatory, and musculoskeletal limitations which affect the performance of external work.

deconditioning. This dilemma will always exist in the field of exercise assessment because the physiological consequences of these two conditions are similar. The best way to resolve this dilemma is by using exercise prescription and repeated testing to reveal how much of the physiological abnormality is reversible.

Disorders of ventilation

Diseases of the lungs and respiratory muscles are usually characterized by pulmonary function testing as being either obstructive (e.g., asthma and chronic bronchitis) or restrictive (e.g., pulmonary fibrosis or respiratory muscle weakness). Unfortu-