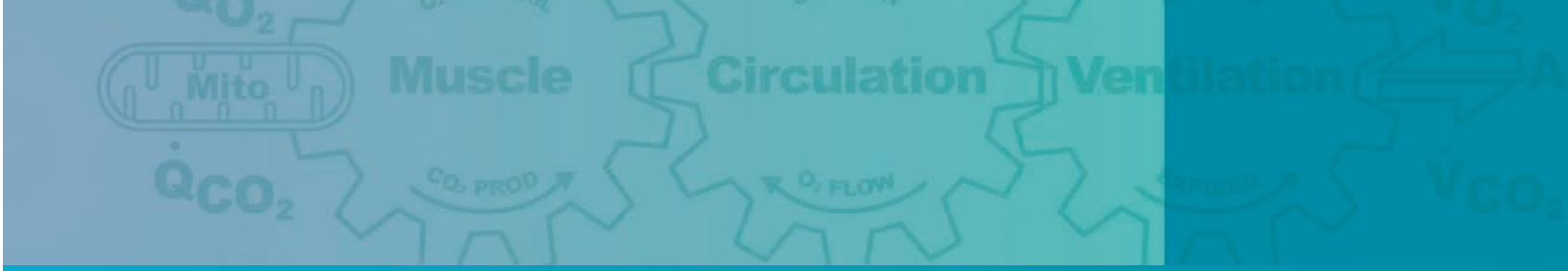
Principles of Exercise Testing and Interpretation

Including Pathophysiology and Clinical Applications

Fifth Edition



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Two Commerce Square
2001 Market Street
Philadelphia, PA 19103 USA
LWW.com

Printed in China

Library of Congress Cataloging-in-Publication Data
9781609138998
1609138996

Principles of exercise testing and interpretation : including pathophysiology and clinical applications / Karlman Wasserman ... [et al.]. — 5th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-60913-899-8 (hardback : alk. paper)
I. Wasserman, Karlman.
[DNLM: 1. Exercise Test. 2. Physical Exertion—physiology. WG 141.5.F9]

616.1'20754—dc23
2011036549

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To Our Families

Preface

In this fifth edition of *Principles of Exercise Testing and Interpretation,* as in earlier editions, we attempt to develop conceptual advances in the physiology and pathophysiology of exercise, particularly as related to the practice of medicine. The underlying theme of the book continues to be the recognition that the most important requirement for exercise performance is transport of oxygen to support the bioenergetic processes in the muscle cells (including, of course, the heart) and elimination of the carbon dioxide formed as a byproduct of exercise metabolism. Thus, appropriate cardiovascular and ventilatory responses are required to match those of muscle respiration in meeting the energy demands of exercise.

As depicted by the logo on the book cover, normal exercise performance requires an efficient coupling of external to internal (cellular) respiration. Appropriate treatment of exercise intolerance requires that patients' symptoms be thought of in terms of a gas exchange defect between the cell and the environment. The defect may be in the lungs, heart, peripheral or pulmonary circulations, the muscles themselves, or there may be a combination of defects. Thus, we describe the pathophysiology in gas transport and exchange that affect any site in the cardiorespiratory coupling between the lungs and the muscles.

We illustrate how cardiopulmonary exercise testing can provide the means for a critical evaluation by the clinician-scientist of the functional competency of each component in the coupling of cellular to external respiration, including the cardiovascular system. To achieve this, clinical cases are used to illustrate the wide spectrum of pathophysiology capable of causing exercise intolerance.

The primary symptoms causing exercise intolerance, typically dyspnea and/or fatigue, are shown to have a rational pathophysiological basis. Without cardiopulmonary exercise testing, the treatment of patients with exercise intolerance may be improperly focused because the pathophysiology causing the exercise intolerance may not be well understood by the physician working within the diagnostic spectrum of his or her subspecialty. Exertional dyspnea and/or fatigue at unusually low levels of exercise can often be traced to abnormal coupling of the cardiopulmonary mechanisms required for normal gas exchange. Therefore, by measuring gas exchange during cardiopulmonary exercise tests, not only can the exercise limitation be quantified, but the functional adequacy of the heart, circulatory system, and lungs also can be established. Fortunately, this can usually be done noninvasively.

We believe that each chapter of this book makes original contributions to the understanding of exercise physiology. In particular, Chapters 2, 3, 4, 5, and 10 provide extensive information about changes in arterial, mixed venous, and femoral vein blood gases and arterial lactate during lower extremity exercise. These chapters are valuable for differentiating the function of the peripheral from central circulations and describe mechanisms that enable favorable shifts in the oxyhemoglobin and CO_2 dissociation curves to optimize arterial-venous differences and minimize changes in muscle capillary P_{O_2} and P_{CO_2}.

The gas exchange responses to exercise can indicate to the investigator which organ(s) are functioning poorly and which are functioning well. Because the pattern of the gas exchange response is characteristic of the disease process, it can enable a clinical diagnosis. For instance, cardiopulmonary exercise testing might not only detect cardiovascular limitation, but could also be used to distinguish which cardiovascular disease restricts the patient's exercise performance when several might coexist, such as coronary artery disease, chronic heart failure, and peripheral vascular disease. Chapter 8 describes a flowchart approach to assist in making a clinical diagnosis, using the physiological data obtained during cardiopulmonary exercise testing. It is likely that no test in medicine can be used to diagnose the broad spectrum of diseases, while quantifying severity of organ dysfunction or improvement in the pathophysiology of exercise intolerance, better and more cheaply than cardiopulmonary exercise testing. As a referral center for problematic cases, we are often impressed with the revelations of pathophysiology provided by cardiopulmonary exercise testing.

This book describes how to evaluate the patient with exercise intolerance using the physiology and pathophysiology of exercise gas exchange as frames of reference. The absence of detailed electrocardiographic displays in this book should not be interpreted to mean that the authors do not regard the electrocardiogram (ECG) to be an essential component of exercise testing. On the contrary, we routinely record and analyze a 12-lead ECG throughout the exercise test. However, interpretation of the exercise ECG is beyond the scope of this book and is thoroughly covered elsewhere. We therefore only provide the interpretation of the ECG records in the case discussions in Chapter 10.

To provide important background information on the interpretation of exercise tests, we devote the first three chapters to the bioenergetic and physiological principles underpinning exercise performance. We apply this knowledge to establish specific variables that can be used to detect abnormalities in function during exercise in Chapter 4. The pathophysiology of exercise limitation

caused by diseases of the cardiovascular, respiratory, musculoskeletal, and other systems is presented in Chapter 5. Chapter 6 describes how to prepare the patient for and how to perform a cardiopulmonary exercise test, with Chapter 7 providing an analysis of normal gas exchange values in both adults and children. In Chapter 8, an interpretive approach for making specific diagnoses is presented, using flowcharts and physiological data derived from the cardiopulmonary exercise test. Chapter 9 describes the expanding applications in which the uses of cardiopulmonary exercise testing have been applied. Importantly, this chapter describes certain clinical diagnoses that can *only* be made by cardiopulmonary exercise testing. The final chapter consists of 110 cases (80 in the book and 30 online) in which cardiopulmonary exercise tests have been of diagnostic and/or therapeutic value. Each was a referral case, studied to answer a specific clinical question, or selected to make a teaching point with respect to the pathophysiology of specific diseases.

Detailed practical information is provided in the appendices to assist in the technical support of a new laboratory, testing the subject, and making necessary calculations. Although of special importance to anyone wishing to establish a laboratory, this information can also be very helpful to the interpreter's understanding of the technical aspects of the measurements and calculations used in cardiopulmonary exercise testing.

We designed the content of this book to help cardiologists, pulmonologists, and exercise physiologists maximize the knowledge gained from computerized measurements of gas exchange during exercise. Thus, it is designed as a guide for those who wish to use cardiopulmonary exercise testing to (1) diagnose the pathophysiology of exercise limitation; (2) evaluate the severity of a patient's pathophysiology; (3) evaluate the effect of medical or surgical therapy; and (4) provide a physiological basis for assessing training strategies for patients undergoing exercise rehabilitation or athletes in training. This book spans the field of exercise from teaching basic concepts in exercise physiology to providing a meaningful report for the medical record. Our goal was to write a comprehensive yet practical book that could be used for multiple purposes by physiologists, cardiologists, pulmonologists, other physicians, and exercise technicians.

Acknowledgments

We are very much indebted to Leah Kram for her highly intelligent editing of the chapters of this fifth edition, as she has for prior editions. Her dedication to this book made its completion possible in a timely fashion.

We are also indebted to William L. Beaver, PhD, for the analysis of oscillatory gas exchange of Case 14 of Chapter 10.

We also want to express our gratitude to Dr. Dan M. Cooper, Professor of Pediatrics at the University of California at Irvine, California, for his excellent contribution to the section on exercise gas exchange in normal children in Chapter 7.

In addition, we would like to express our appreciation to Piergiuseppe Agostoni, Professor of Cardiology at the University of Milan, Milan, Italy, for his overreading and helpful suggestions on the heart failure section in Chapter 5.

Finally, we are grateful to our colleagues, our former fellows and students, and the many physicians and scientists who have participated in our semiannual postgraduate course (practicum) in exercise testing and interpretation over the last 29 years, for which the four prior editions served as a syllabus. This fifth edition benefits from the many useful discussions we have had with former course participants, as well as the knowledge gained from new research. These have served as a milieu for improving our understanding of exercise physiology and pathophysiology and have helped to close the gap between physiologic knowledge and the application of cardiopulmonary exercise testing to solve clinical problems.

K.W. is especially indebted to his wife, Gail, for tolerating his diversions during innumerable evenings and weekends in his effort to see this edition completed.

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CHAPTER

1

Exercise Testing and Interpretation

The energy to support life, with its changing levels of physical and metabolic activity, is obtained from the oxidation of metabolic substrate. Oxygen (O_2) is the key that unlocks the energy from metabolic substrate by serving as the proton acceptor in the oxidative processes that yield high-energy compounds. The energy is located in the bond(s) of a phosphate anion in high-energy compounds, mainly as adenosine triphosphate (ATP). Splitting of these high-energy phosphate bonds (~P) is controlled by enzymatic reactions at the myofibril such that the energy released is transduced into mechanical energy for muscular contraction.

Because the reserve of ~P in the cell is quite small relative to the needs, ~P production—and therefore O_2 consumption—must increase to sustain exercise. Because there is a relatively precise relation between the O_2 consumption and ~P production, measurement of O_2 consumption provides insight into the rate of ~P expended for physical work.

CELL RESPIRATION AND BIOENERGETICS

The most immediate requirement of exercise is the release of the energy of the terminal ~P of ATP to fuel its energy demands. The bioenergetic processes for the regeneration of ATP in the muscle is achieved by three mechanisms (Fig. 1.1): aerobic (O_2-requiring) oxidation of substrates (primarily glycogen and fatty acids), anaerobic hydrolysis of creatine phosphate (phosphocreatine, PCr), and anaerobic (non-O_2-requiring) oxidation of glycogen or glucose by pyruvate to yield lactic acid—or, more precisely, the lactate ion and its associated proton. Each of these processes is critically important for the normal exercise response, and each plays a different role in the total bioenergetic response.

The aerobic oxidation of carbohydrate and fatty acids provides the major source of ATP regeneration and becomes the unique source in the steady state of moderate-intensity exercise. In a normally nourished individual, about five-sixths of the energy comes from aerobic oxidation of carbohydrate and one-sixth comes from fatty acids.[3,8,20] To sustain a given level of exercise, the cardiorespiratory response must be adequate to supply the O_2 needed to regenerate, aerobically, all the ATP needed for the activity. Local stores of PCr are a source of high-energy phosphate in the early phase of exercise and account for much of the O_2 deficit during the first minutes of exercise and the recovery repayment of the O_2 debt.[7,16] PCr is rapidly hydrolyzed by creatine (Cr) kinase to Cr and inorganic phosphate (Pi). The energy released in this reaction is used to regenerate ATP at the myofibril during early transient phase of exercise (Fig. 1.2). Subjects with less fitness for aerobic exercise have a greater decrease in PCr at a given work rate, or O_2 consumption, than a more fit subject. PCr, like adenosine diphosphate, is intimately linked to the control of O_2 consumption. Thus, the profile of change of PCr is often considered to be a proxy

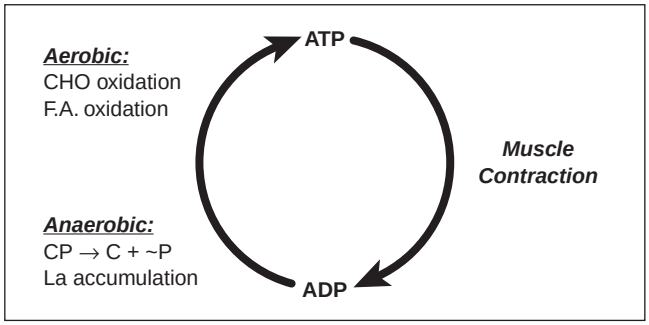

FIGURE 1.1. Sources of energy for adenosine triphosphate (ATP) regeneration from adenosine diphosphate (ADP). CHO, carbohydrate; FA, fatty acid; CP, creatine phosphate.

variable of muscle O_2 consumption during the early period of exercise when its intracellular concentration is changing.[2,6,13,16]

During the process of glycolysis, the coenzyme nicotinamide adenine dinucleotide (NAD^+) is reduced to $NADH + H^+$. If it is not reoxidized aerobically at the mitochondrial site of O_2 utilization, $NADH + H^+$ can be reoxidized anaerobically by pyruvate ($NADH + H^+ + pyruvate \rightarrow NAD^+ + lactate$). Thus, pyruvate can serve as the oxidant to regenerate NAD^+ when the cell becomes O_2 poor. The reoxidation of $NADH + H^+$ to NAD^+ is required for glycolysis to proceed.

The energy produced by anaerobic glycolysis is relatively small per unit of glycogen and glucose consumed. Two molecules of lactate are produced with the consumption of each six-carbon moiety of glycogen or glucose molecule. Because an H^+ is produced with each lactate ion that accumulates, anaerobic glycolysis has important implications with respect to acid–base balance, buffering of lactic acid, hydrogen ion regulation, and gas exchange during exercise. Gas exchange (O_2 uptake [$\dot{V}O_2$] and CO_2 output [$\dot{V}CO_2$]) is affected in a different way by each of the three sources of ATP regeneration (oxidation of carbohydrate and fatty acids, splitting of PCr and anaerobic glycolysis). For instance, when the regeneration of ATP is aerobic, O_2 is consumed and carbon dioxide (CO_2) is produced in proportion to the ratio of carbohydrate to fatty acid in the substrate being oxidized in the muscle cells. On the other hand, when PCr is split, it is converted to Cr and Pi. Because Cr is neutral in water, whereas PCr reacts like a relatively strong acid, the splitting of PCr decreases cell acidity. This reaction, therefore, consumes CO_2 produced from cellular metabolism by its conversion to bicarbonate (HCO_3^-) in the tissues.[15,26] This reduces CO_2 output at the airway relative to O_2 uptake, creating a disparity between the early kinetics in $\dot{V}CO_2$ relative to $\dot{V}O_2$ (to be discussed more thoroughly in Chapter 2).[7,27] Finally, when high-energy phosphate is generated from anaerobic glycolysis, the H^+ produced with lactate is buffered predominantly by HCO_3^-, thereby "consuming" HCO_3^- and adding CO_2 to that produced by aerobic metabolism. This is usually sufficient to increase $\dot{V}CO_2$ above $\dot{V}O_2$.

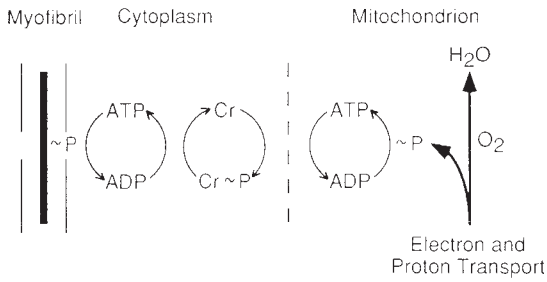

FIGURE 1.2. Scheme by which phosphocreatine (creatine phosphate, PCr or Cr~P) supplies high-energy phosphate (~P) to adenosine diphosphate (ADP) at the myofibril. Because of its quantity in muscle, PCr serves as a reservoir of readily available ~P as well as a shuttle mechanism to translocate ~P from mitochondria to the myofibril contractile sites. ATP, adenosine triphosphate.

Because these different mechanisms in ATP regeneration have different effects on gas exchange, study of the gas exchange responses to exercise can reveal information regarding the kinetics of the relative contributions of aerobic respiration, PCr hydrolysis, and anaerobic glycolysis to the total bioenergetic response.

WHY MEASURE GAS EXCHANGE TO EVALUATE CARDIOVASCULAR FUNCTION AND CELLULAR RESPIRATION?

Physical exercise requires the interaction of physiological control mechanisms to enable the cardiovascular and ventilatory systems to couple their behaviors to support their common function—that of meeting the increased respiratory demands (O_2 consumption [$\dot{Q}O_2$] and CO_2 production [$\dot{Q}CO_2$]) of the contracting muscles (Fig. 1.3). Thus, both systems are stressed during exercise to meet the increased need for O_2 by the contracting muscles and the removal of metabolic CO_2. Therefore, by studying external respiration in response to exercise, it is possible to address the functional competence or "health" of the organ systems coupling external to cellular respiration.

Cardiopulmonary exercise testing (CPET) offers the investigator the unique opportunity to study the cellular, cardiovascular, and ventilatory systems' responses simultaneously under precise conditions of metabolic stress. Exercise tests in which gas exchange is not determined cannot realistically evaluate the ability of these systems to subserve their common major function, which is support of cellular respiration. CPET allows the investigator to distinguish between a normal and an abnormal response characteristic of disease, grade the adequacy of the coupling mechanisms, and assess the effect of therapy on a diseased organ system. However,

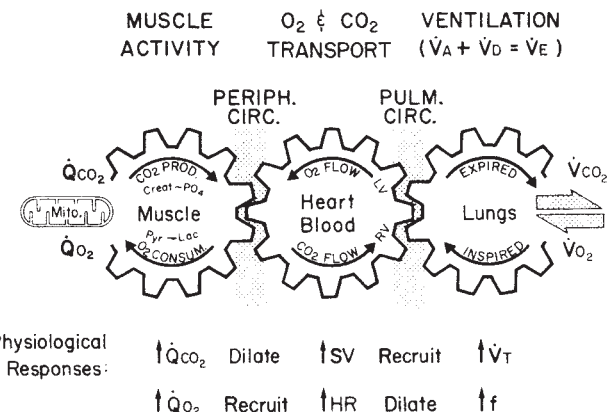

FIGURE 1.3. Gas transport mechanisms for coupling cellular (internal) to pulmonary (external) respiration. The gears represent the functional interdependence of the physiologic components of the system. The large increase in oxygen (O_2) utilization by the muscles ($\dot{Q}O_2$) is achieved by increased extraction of O_2 from the blood perfusing the muscles, the dilatation of selected peripheral vascular beds, an increase in cardiac output (stroke volume and heart rate), an increase in pulmonary blood flow by recruitment and vasodilatation of pulmonary blood vessels, and finally, an increase in ventilation. Oxygen is taken up ($\dot{V}O_2$) from the alveoli in proportion to the pulmonary blood flow and degree of O_2 desaturation of hemoglobin in the pulmonary capillary blood. In the steady state, $\dot{V}O_2 = \dot{Q}O_2$. Ventilation [tidal volume (V_T) × breathing frequency (f)] increases in relation to the newly produced CO_2 ($\dot{Q}CO_2$) arriving at the lungs and the drive to achieve arterial CO_2 and hydrogen ion homeostasis. These variables are related in the following way: $\dot{V}CO_2 = \dot{V}A \times PaCO_2/PB$, where $\dot{V}CO_2$ is minute CO_2 output, $\dot{V}A$ is minute alveolar ventilation, $PaCO_2$ is arterial or ideal alveolar CO_2 tension, and PB is barometric pressure. $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{Q}O_2$, and $\dot{Q}CO_2$ are expressed as standard temperature pressure dry (STPD).

The representation of uniformly sized gears is not intended to imply equal changes in each of the components of the coupling. For instance, the increase in cardiac output is relatively small for the increase in metabolic rate. This implies an increased extraction of O_2 from and CO_2 loading into the blood by the muscles. In contrast, at moderate work intensities, minute ventilation increases in approximate proportion to the new CO_2 brought to the lungs by the venous return. The development of metabolic acidosis at heavy and very heavy work intensities accelerates the increase in ventilation to provide respiratory compensation for the metabolic acidosis.

not only is it the most effective in this regard, but CPET is also one of the most inexpensive ways of diagnosing the pathophysiology of the cardiovascular and ventilatory systems.

In contrast to other diagnostic tests that evaluate one organ system, CPET evaluates each and every organ system essential for exercise simultaneously. An exercise test that restricts its observations to the electrocardiogram (ECG) can only support a diagnosis of myocardial ischemia. However, this is imperfect with respect to sensitivity and specificity. Furthermore, an individual patient may have mixed defects (e.g., cardiac and pulmonary). CPET can be used to determine which of these defects is (or is predominantly) responsible for the patient's symptoms before embarking on major therapeutic procedures directed at either one.[31]

NORMAL COUPLING OF EXTERNAL TO CELLULAR RESPIRATION

Figure 1.3 schematizes the coupling of pulmonary ($\dot{V}O_2$ and $\dot{V}CO_2$) to cellular ($\dot{Q}O_2$ and $\dot{Q}CO_2$) respiration by the circulation. Obviously, the circulation must increase at a rate that is adequate to meet the O_2 requirement ($\dot{Q}O_2$) of the cells, and so cardiac output increases in proportion to the $\dot{Q}O_2$. In normal subjects, in the steady state, muscle blood flow must increase by approximately 5 to 6 liters per liter of O_2 consumption,[24,32] depending on the hemoglobin concentration. Since 5 liters of arterial blood contain approximately 1 liter of O_2 when the hemoglobin concentration is 15 g per dL, the normal steady-state circulatory response must exceed this flow to meet the energy requirement. O_2 cannot be completely extracted from the muscle blood flow since a gradient for O_2 diffusion must be maintained between the end-capillary blood and myocyte[24]: If $\dot{V}O_2$ fails to increase at a rate appropriate to $\dot{Q}O_2$, such as seen in diseases of the cardiovascular system,[10,33] lactic acidosis will be a necessary consequence and often at a low work rate.

Because the body's total H^+ is only on the order of 3.4 µmol, and the total H^+ equivalent produced per minute from metabolism in the form of CO_2, even for a moderate walking speed, is about 40,000 µmol/minute (approximately 10,000 times), elimination of the increased CO_2 must be accomplished quickly and precisely. Therefore, to regulate arterial pH at physiological levels, the ventilatory control mechanism(s) must increase ventilation at a rate closely linked to the CO_2 exchanged at the lungs and the degree of lactic acidosis. Thus, the ventilatory control system is closely linked to the CO_2-H^+ and lactic acid production during exercise, with ventilation increasing sufficiently to regulate arterial H^+. There is little deviation in the normal H^+ response in humans because the ventilatory control mechanisms constrain the arterial H^+ increase. A very slight respiratory acidosis, but typically not an alkalosis, can be encountered in normal subjects during the non–steady state of moderate exercise[19] and a metabolic acidosis is characteristic at heavier work intensities. Ventilation must, therefore, increase at a greater rate, relative to work rate, when a lactic acidosis is superimposed on the respiratory acid (CO_2) load. This is necessary to meet the demands of clearing the additional CO_2 produced by the HCO_3^- buffering of the lactic acid. However, to reduce arterial PCO_2 in order to constrain the fall in pH, ventilation must increase at an even greater rate than $\dot{V}CO_2$.[29] However, the hyperventilatory response is typically inadequate to

avoid the development of arterial acidemia when lactate increases during exercise.[28]

WHAT IS CARDIOPULMONARY EXERCISE TESTING?

CPET is an examination that allows the investigator to simultaneously study the responses of the cardiovascular and ventilatory systems to a known exercise stress. This is possible because gas exchange at the airway is a consequence of cardiac output and pulmonary blood flow, as well as peripheral O_2 extraction coupled to ventilation. Thus, the heart, with the circulation, couples gas exchanges (O_2 and CO_2) of muscle respiration with that at the lungs. The adequacy of the cardiovascular transport of O_2 for known exercise work rates is described by the lung gas exchange.

For CPET, the gas exchange measurements are accompanied by the ECG, heart rate, and blood pressure measurements. Importantly, the cardiovascular measurements are interrelated with the gas exchange measurements. The interrelation adds meaning to the non–gas exchange measurements because it relates them to the actual energy expended during exercise rather than relying on indirect estimates. It also provides information regarding the stroke volume response to exercise by the measure of the O_2 extracted from each heartbeat at specified work intensities.

CARDIAC STRESS TEST AND PULMONARY STRESS TEST: NOMENCLATURE FALLACIES

The authors would like to dispel a concept that remains prevalent in clinical exercise testing—namely, that there is cardiac stress testing and pulmonary stress testing. It is impossible to stress only the heart or only the lungs with exercise. Both the heart and lungs are needed to support the respiration of all living cells of the body and to maintain their energy requirements. The function of the heart, the lungs, and the peripheral and pulmonary circulations need to be coordinated in order to meet the increased cellular respiratory demands of exercise. Diseases of the heart cause both abnormal breathing and gas exchange responses to exercise, as do disorders of the lungs. However, the patterns of the abnormal responses are usually different. This will be described in later chapters.

Abnormalities of the heart might cause abnormalities in lung gas exchange during exercise, with "pulmonary symptoms."[11,14,22,30] Similarly, pulmonary disorders might result primarily in abnormalities in cardiovascular responses to exercise because the heart is in the chest and lung disease can limit cardiac filling, either because of increased pulmonary vascular resistance or extreme changes in intrathoracic pressure during breathing.[4,9] Although the cardiovascular and pulmonary gas exchange responses to exercise tend to be relatively uniform and, to a large extent, predictable in normal subjects, specific diseases affect the gas exchange responses in specific ways, depending on the particular pathophysiology. Thus, the knowledgeable examiner cannot only detect abnormality, but can often define the contributory disease process. Because CPET is quantitative, it also allows the severity of dysfunction to be graded. It is our impression that, in contrast to Japan and Europe, CPET is a greatly underutilized diagnostic tool in the United States. Likely, a great deal of money is wasted by performing available tests, which are not physiologically qualitative or quantitative in the diagnostic process, in contrast to CPET. It is often not appreciated that $\dot{V}O_2$ is equal to cardiac output (a cardiac function) and arterial-venous O_2 difference (a cardiac and peripheral vascular function).

PATTERNS OF CHANGE IN EXTERNAL RESPIRATION (OXYGEN UPTAKE AND CARBON DIOXIDE OUTPUT) AS RELATED TO FUNCTION, FITNESS, AND DISEASE

This book is devoted largely to describing patterns of gas exchange that relate to function, fitness, and disease states. As described earlier, increases in external respiration ($\dot{V}O_2$ and $\dot{V}CO_2$) need to be intimately coupled to the increases in cellular respiration ($\dot{Q}O_2$ and $\dot{Q}CO_2$).

The proportional contributions of aerobic and anaerobic regeneration of ATP during exercise can often be inferred from measurements of external respiration. For example, gas exchange kinetics differ in response to exercise depending on whether work is performed above or below the anaerobic threshold (*AT*) (Fig. 1.4). For work performed below the *AT* (without a lactic acidosis), O_2 flow through the muscles is adequate to supply all of the O_2 needed for the aerobic regeneration of ATP in the steady state, and the patterns of $\dot{V}O_2$ and $\dot{V}CO_2$ increase as shown in the right side of the *Without Lactic Acidosis* panel of Figure 1.4. In contrast, if the O_2 supply is inadequate to meet the total O_2 need, lactic acidosis develops and the patterns of increase in $\dot{V}O_2$ and $\dot{V}CO_2$ change as shown in the right side of the *With Lactic Acidosis* panel of Figure 1.4. In the former state, work is done in a true steady state, in which $\dot{V}O_2$ is equal to $\dot{Q}O_2$. In the latter state, the cardiopulmonary system fails to transport enough O_2 to meet the cellular O_2 requirement, $\dot{V}O_2$ does not reach a steady state and work is performed with a lactic acidosis. Consequently, $\dot{V}CO_2$ increases in excess of $\dot{V}O_2$ due to the CO_2 release from HCO_3^- as it buffers lactic acid.

Individuals who are fit for endurance work do not develop a lactic acidosis until work rates are high relative

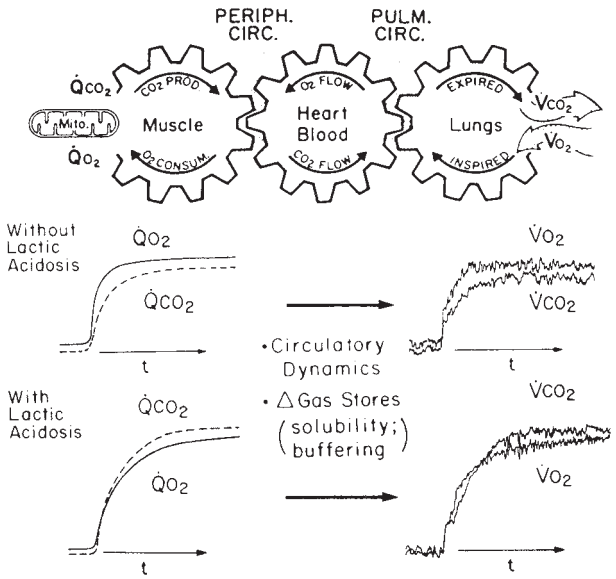

FIGURE 1.4. Scheme of coupling of external to cellular respiration for constant-load exercise. The right side of the figure shows breath-by-breath data for 6 minutes of constant work rate exercise for work with and without lactic acidosis. Each study is an overlay of four repetitions to reduce random noise in the data and enhance the physiological features. Measurements of external respiration (right) can be used as a basis for reconstructing the changes in muscle cellular respiration. The left side of the figure shows, schematically, the changes in muscle cellular respiration that would account for the observed changes in external respiration. The factors that modulate the relationship between cellular respiration and external respiration are shown in the center. At the start of exercise, there is normally a step increase in both $\dot{V}O_2$ and $\dot{V}CO_2$ consequent to the abrupt increase in pulmonary blood flow due to an immediate increase in heart rate and stroke volume. After an approximate 15-second delay, $\dot{V}O_2$ and $\dot{V}CO_2$ increase further when venous blood formed after exercise started, arrives at the lungs. At this early time, $\dot{V}CO_2$ increases more slowly than $\dot{V}O_2$. The slower rise in $\dot{V}CO_2$ than $\dot{V}O_2$ is accounted for by utilization of CO_2 in the production of HCO_3^- associated with release of K^+ by the muscle cell associated with the splitting of PCr and perhaps other chemical reactions in the tissues that store some of the metabolic CO_2. For work rates without a lactic acidosis, $\dot{V}O_2$ reaches a steady state by approximately 3 minutes and $\dot{V}CO_2$ by 4 minutes. For work rates with a lactic acidosis, $\dot{V}O_2$ does not reach a steady state by 3 minutes and may not reach a steady state before the subject fatigues. In contrast, $\dot{V}CO_2$ kinetics remain relatively unchanged, with the level of $\dot{V}CO_2$ exceeding $\dot{V}O_2$ after the first several minutes of heavy-intensity exercise (see text for discussion of mechanisms).

to less fit subjects. Their $\dot{V}O_2$ kinetics are relatively rapid compared to less fit subjects.[17] Patients with circulatory disorders usually have slow $\dot{V}O_2$ kinetics, even at relatively low work rates.[12] Thus, the difference between the steady-state $\dot{V}O_2$ requirement and the actual $\dot{V}O_2$ during the transition from rest to exercise (i.e., the O_2 deficit) varies depending on the subject's fitness for aerobic work.

FACTORS LIMITING EXERCISE

Symptoms that stop people from performing exercise are fatigue, dyspnea, and/or pain (e.g., angina or claudication). By observing external respiration during a quantitative exercise test in which large muscle groups are stressed (walking, running, or cycling), it can be determined if exercise tolerance is reduced and, if so, whether abnormal cardiovascular, ventilatory, or metabolic responses to exercise account for the reduction.

Fatigue

A muscle is considered to fatigue when its force output decreases for a given stimulus. However, the exact mechanisms of muscle fatigue remain a topic of debate. Because lactic acidosis accompanies an increased rate of anaerobic ATP production and the Pi concentration increases in proportion to the time constant of the $\dot{V}O_2$ change, it is tempting to attribute the fatigue to the intracellular consequences of these mediators and possibly decreased levels of ATP. Low cellular pH and increased Pi have been shown to reduce force production via reduction of myofibrillar calcium sensitivity and impaired calcium release from the sarcoplasmic reticulum. However, regardless of the precise mechanisms,[11] the consistent physiological signal for impending fatigue during exercise is the failure of $\dot{V}O_2$ to reach a steady state and to meet the cellular O_2 requirement.

A number of investigators have measured $\dot{V}O_2$ during increasing work rate exercise in both patients with heart failure and normal subjects[10,21,33] and observed that $\dot{V}O_2$ increases more slowly, relative to the increase in work rate, before the onset of fatigue. This places further demands on anaerobic mechanisms of ATP regeneration. Although this phenomenon is seen as work rate is increased toward peak $\dot{V}O_2$ in normal subjects, it is particularly notable in heart failure patients as they approach their symptom-limited maximum work rate.

Dyspnea

Dyspnea is a common exercise-induced symptom of disease states. It occurs in patients with pathophysiology that results in inefficient gas exchange due to ventilation–perfusion mismatching (high physiological dead space), low work rate lactic acidosis (e.g., low cardiac output response to exercise), exercise-induced hypoxemia, and disorders associated with impaired ventilatory mechanics. These pathophysiological changes can occur singly, but more commonly they occur in combinations. For example, patients with chronic obstructive pulmonary disease have a combination of impaired ventilatory mechanics that limits their maximal ability to ventilate their lungs and ventilation–perfusion mismatching that causes ventilation to be inefficient in eliminating CO_2-H^+ equivalents from

the body. In addition, they may have exercise-induced hypoxemia that further stimulates ventilatory drive.

Dyspnea also occurs in patients with left ventricular failure. These patients have a low work rate lactic acidosis, as well as inefficient lung gas exchange due to ventilation–perfusion mismatching (high physiologic dead space). Both of these mechanisms stimulate ventilatory drive consequent to the inefficient elimination of CO_2-H^+ equivalents from the body. Any pathophysiology that increases ventilatory drive can cause dyspnea.

Arterial hypoxemia is a common disorder in lung and pulmonary vascular diseases. If the oxygen tension decreases during exercise, it stimulates the carotid body chemoreceptors to increase ventilatory drive. This stimulus to ventilation can cause the symptom of dyspnea. The carotid bodies are chemoreceptors that drive ventilation in response to both exercise arterial hypoxemia and in acidemia.[29] Mechanisms of dyspnea in health and disease are discussed further in later chapters.

Pain

Pain in the chest, arm, or neck is the most common symptom of acute myocardial ischemia brought on by exercise (angina pectoris) in patients with coronary artery disease. This is a reflection of an inadequate O_2 supply to the myocardium relative to the myocardial O_2 demand. Reducing the O_2 demand by decreasing myocardial work or increasing myocardial O_2 supply can eliminate anginal pain. These are established cardiologic therapeutic practices for treating anginal pain. The successful treatment of myocardial ischemia might be documented with CPET.

Claudication occurs because of an O_2 supply–demand imbalance in the muscles of the lower exercising extremities. Walking at a normal pace requires an increase in $\dot{Q}O_2$ of the muscles of locomotion of approximately 20-fold compared to rest. Therefore, the ability of muscle blood flow to increase appropriately is critically important to enable walking without ischemic pain. If stenotic, atherosclerotic changes in the conducting vessels to the lower extremity limit the increase in leg blood flow in response to exercise, an O_2 supply–demand imbalance will occur. This will result in critically low levels of O_2 in the muscles,[5] causing local K^+, lactate, and H^+ accumulation secondary to the ischemia. These accumulated metabolites are likely mediators of the exercise-induced leg pain. The impaired blood supply will be reflected in slow O_2 uptake kinetics.[1]

EVIDENCE OF SYSTEMIC DYSFUNCTION UNIQUELY REVEALED BY INTEGRATIVE CARDIOPULMONARY EXERCISE TESTING

Chapter 9 describes pathophysiologic diagnoses uniquely made by CPET. Obligatory changes in the normal exercise gas exchange responses occur when diseases of the cardiovascular or ventilatory systems, or both, decrease their effective functioning. Thus, the gas exchange responses to exercise could indicate which organ(s) are functioning poorly and which are functioning well. CPET provides the means not only to distinguish between lung and cardiovascular disease, but also to distinguish one cardiovascular disease from another as the cause of exercise limitation. For instance, coronary artery disease, chronic heart failure, and peripheral vascular disease have abnormal patterns of exercise gas exchange unique to each and, therefore, can be distinguished from each other.[25] The gas exchange measurements can confirm ischemia-induced left ventricular dysfunction during exercise and the precise metabolic rate at which the ischemia and dysfunction take place. The unique ability of CPET to detect pulmonary vasculopathy leading to pulmonary hypertension early in the course of disease, and to detect an exercise-induced right-to-left shunt, is addressed in Chapters 5 and 9.[23]

The CPET in which gas exchange is measured with the ECG, should be among the most sensitive tests to evaluate causes of exercise intolerance because exercise amplifies the abnormal manifestations of the organs that couple external to cellular respiration (see Fig. 1.3). Also, no test is likely to be capable of quantifying improvement or worsening of these functions with greater sensitivity than a CPET. Thus, CPET—with gas exchange, ECG, blood pressure, and spirometric measurements—early in the evaluation of the patient with exercise limitation would greatly reduce utilization of less sensitive diagnostic tests, thereby decreasing medical costs. However, maximal benefit cannot be obtained from a CPET unless the diagnosing physician is trained to recognize both the normal responses to exercise and the pathophysiological changes brought about by disease states.

To facilitate recognition of the pattern of disease, we believe that the data collected during a cardiopulmonary exercise study should be displayed graphically, so that the relationships between the functional variables can be seen. We illustrate this approach in Chapter 10, showing CPET data from patients with a large variety of diseases. A nine-panel graphical display was developed to view critical variables simultaneously. This nine-panel graphical array is shown on a single page to provide a picture of critical data needed to determine the physiologic state of each of the links in the coupling of external to cellular respiration. It was developed over time from an extensive practice experience.

CPET makes important contributions to the diagnosis and treatment of patients, is relatively inexpensive, and has a low morbidity. Therefore, it is surprising that it is not used more frequently by specialists who treat patients with heart and lung diseases. Nevertheless, we do recognize that it is becoming used with a greater frequency than in preceding years. We believe that it is likely that its greater

use in the future will result from the recognition that it shortens time to diagnosis and reduces medical costs.

SUMMARY

Organ dysfunction that limits exercise can usually be detected by evidence of an abnormality in the coupling of external (pulmonary) respiration to cellular respiration. Integrative CPETs in which gas exchange is measured dynamically at the airway rather than as a single steady-state measurement, can usually identify the pathophysiology of reduced exercise tolerance. Discerning the pathophysiology of the intolerance is often sufficient to make an anatomical diagnosis. If not, it can suggest other tests that could narrow the diagnostic choices. When the cause of the patient's exercise intolerance is not clinically obvious, we believe that it is cost-effective to perform a CPET before proceeding with more invasive and expensive testing. As stated by the European Society of Cardiology, "The full potentials of CPET in the clinical and research setting still remain largely underused."[18] Often new insights are obtained into the disease processes of patients, particularly in those patients with cardiovascular diseases. Possibly, CPET covers a broader range of potential diagnoses than any test in medicine. Furthermore, it "amplifies" the manifestation of the basic disease process, which thereby assists in the differential diagnosis of diseases with similar symptoms.

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CHAPTER

2

Physiology of Exercise

The performance of muscular work requires the physiological responses of the cardiovascular and ventilatory systems to be coupled with the increase in metabolic rate; efficient coupling minimizes the stress to the component mechanisms supporting the energy transformations. In other words, cellular respiratory (internal respiration) requirements can only be met by the interaction of physiological mechanisms that link gas exchange between the cells and the atmosphere (external respiration) (see Fig. 1.3). Inefficient coupling increases the stress to these systems and, when sufficiently severe, can result in symptoms that impair or limit work performance. Efficient gas exchange between the cells and the environment requires the following:

- Appropriate intracellular structure, energy substrate, and enzyme concentrations
- A heart capable of pumping the quantity of oxygenated blood needed to sustain the energy transformations
- An effective system of blood vessels that can selectively distribute blood flow to match local tissue gas exchange requirements
- Blood with normal hemoglobin of adequate concentration
- An effective pulmonary circulation through which the regional blood flow is matched to its ventilation
- Normal lung mechanics and chest bellows
- Ventilatory control mechanisms capable of regulating arterial blood gas tensions and hydrogen ion concentration

The response of each of the coupling links in the gas exchange process is usually quite predictable and can be used as a frame of reference for considerations of impaired function.

This chapter reviews the essentials of skeletal muscle physiology, including the relationship between structure and function, cellular respiration, substrate metabolism, and the effect of an inadequate O_2 supply. After considering internal (cellular) respiration, it examines the circulatory and ventilatory links between internal and external respiration, including the factors that determine the magnitude and time course of the cardiovascular and ventilatory responses and how they are coupled to the metabolic stress of exercise. Thus,

this chapter is comprehensive and serves as the underpinning of the interpretation of the clinical problems to follow in subsequent chapters. Because of their multiple applications and relevancies, some subtopics might be repeated under major topics. Therefore, the reader may find the topical outline at the beginning of this chapter to be a useful guide.

SKELETAL MUSCLE: MECHANICAL PROPERTIES AND FIBER TYPES

Human skeletal muscles consist of two basic fiber types: types I and II (Table 2.1). These fiber types are classified on the basis of both their contractile and biochemical properties.[118] Type I (slow-twitch) fibers take a longer time to develop peak tension (≈80 msec) following their activation than type II (fast-twitch) fibers (≈30 msec). The slow contractile properties of type I fibers appear to result largely from the relatively low activity of the myosin ATPase at the myofibril that catalyzes the splitting of the terminal high-energy phosphate of adenosine triphosphate (ATP), the lower Ca^{++} activity of the regulatory protein, troponin, and the slower rate of Ca^{++} uptake by sarcoplasmic reticulum. These same properties appear to confer a relatively high resistance to fatigue on the type I fibers.

Biochemical differences between the two basic fiber types focus chiefly on their capacity for oxidative and glycolytic activities. Type I fibers, being especially rich in myoglobin, are classified as red fibers, whereas type II fibers, which contain considerably less myoglobin, are classified as white fibers. The type I slow-twitch fibers tend to have significantly higher levels of oxidative enzymes than the type II fast-twitch fibers, which typically have a high glycolytic activity and enzyme profile. The type II fibers are further classified into type IIa and type IIx (formerly classified as type IIb),[49] based on the greater oxidative and lesser glycolytic potential of the type IIa fibers compared with the type IIx fibers (Table 2.1). With respect to substrate stores, muscle glycogen concentration is similar in type I and type II fibers, but the triglyceride content is two to three times greater in the type I slow-twitch fibers. Type I slow-twitch fibers may be more efficient than the type II fast-twitch fibers, performing more work or developing more tension per unit of substrate energy utilized.[48]

Considerable potential for change by specific training exists in the enzyme concentrations of a particular fiber. For example, a fast-twitch fiber in an endurance-trained athlete could have higher concentrations of oxidative enzymes than in a chronically sedentary subject.[55] These structural and functional differences between fiber types depend to a large extent on the neural innervation of the fibers. A single motor neuron supplies numerous individual muscle fibers; this functional assembly is termed a *motor unit*. These fibers are distributed throughout the muscle rather than being spatially contiguous. Fibers comprising a motor unit are characteristically of the same fiber type, and substrate depletion occurs rather uniformly within each fiber of the contracting unit.

Fiber type distribution within human skeletal muscle varies from muscle to muscle. For example, the soleus muscle typically has a much higher density of slow-twitch fibers (>80%) than the gastrocnemius muscle (~50%) or the triceps brachii (~20% to 50%). The vastus lateralis muscle (~50% slow-twitch fibers) has been used widely for analysis of fiber type characteristics in humans. The basic fiber type pattern of this muscle varies in different subjects. Elite endurance athletes typically have a high percentage of slow-twitch fibers in this muscle (>90% is not uncommon) compared with untrained control subjects (~50%) or elite sprinters (20% to 30%).

Whereas basic fiber type pattern is genetically determined, it is greatly influenced by the neural characteristics of the efferent motor neuron. When the motor nerves innervating the fast flexor digitorum longus and the slow soleus muscles of the cat are cut and cross-spliced, the contractile and biochemical characteristics of the muscle

Table 2.1

Characteristics of Muscle Fiber Types

	Slow oxidative (type 1)	Fast oxidative (type IIa)	Fast glycolytic (type IIx)
Contraction	Slow twitch	Fast twitch	Fast twitch
Fiber size	Small	Intermediate	Large
Color	Red	Red	White
Myoglobin concentration	High	High	Low
Mitochondrial content	High	High	Low

begin to resemble the features of the muscle originally innervated by the nerve.[20] Thus, an important trophic influence on muscle function is conferred by its nerve supply. Although phenotypic changes within a muscle fiber can be induced by activity, with mechanical factors such as stretch considered to be contributory to the fast-to-slow shift, a typical program of exercise training does not cause appreciable interchanges between type I and type II fibers; however, it can cause changes within type II fibers (e.g., from type IIx to type IIa).[70] Evidence is accumulating, however, that long-term inactivity and/or chronic disease can result in a shift toward a greater percentage of type II fibers.

The pattern of activation of fiber types depends on the form of exercise. For low-intensity exercise, the type I slow-twitch fibers tend to be recruited predominantly, whereas the type II fast-twitch fibers (which produce greater force) are recruited at higher work rates, especially at or above 70% to 80% of the maximal aerobic power.[43] It should be noted that although training increases the percentage of type I fibers in active muscle and detraining reduces it, it is difficult to discern a specific pathophysiology in the gas exchange response to exercise detraining, other than an increase in anaerobic metabolism at a lower work rate.

BIOENERGETICS

Skeletal muscle may be considered to be a machine that is fueled by the chemical energy of substrates derived from ingested food and stored as carbohydrates and lipids in the body. Although protein is a perfectly viable energy source, it is not used to fuel the energy needs of the body to any appreciable extent, except under conditions of starvation.

The free energy of the substrate (i.e., that fraction of the total chemical energy that is capable of doing work) is not used directly for muscle contraction. It must first be converted into and stored in the terminal phosphate bond of ATP. The terminal phosphate bond of this compound has a high free energy of hydrolysis (ΔG) and is designated as a high-energy phosphate bond (~P). Current estimates of ΔG per ~P for physiological conditions such as those occurring in contracting muscle are as high as 12 to 14 Kcal/mole. Therefore, muscle is ultimately a digital device operating in discrete multiple units of ~P energy, with one ~P thought to be used per myosin cross-bridge linkage to and subsequent release from actin. The muscle uses this energy for the conformational changes, externally manifested by shortening or increasing tension. Thus, muscular exercise depends on the structural characteristics of muscle and on the body's systems, which maintain a physicochemical milieu for adequate ATP regeneration.

Sources of High-Energy PO_4 and Cell Respiration

Energy for muscular contraction is obtained predominantly by the oxidation in the mitochondria of three-carbon (pyruvate) and two-carbon (acetate) metabolic intermediaries from carbohydrate and fatty acid catabolism (Fig. 2.1). A small additional amount of energy comes from biochemical mechanisms in the cell cytoplasm that metabolize glucose and glycosyl units (from glycogen) to pyruvate (see Fig. 2.1). Both the mitochondrial and cytosolic sources of energy are transformed into high-energy phosphate compounds, predominantly as creatine phosphate and ATP. During the splitting of ~P from these compounds, energy is released for cellular reactions such as biosynthesis, active transport, and muscle contraction. Exercise entails an acceleration of these energy-yielding reactions in the muscles to regenerate ~P at the increased rate needed for the increased energy expenditure of physical work. Thus, the cellular consumption of O_2 is increased; this must be matched by an increased delivery of O_2 from the atmosphere to the mitochondria. Simultaneously, CO_2, the major catabolic end product of exercise, is removed from the cell by muscle blood flow and eliminated from the body by ventilating the pulmonary blood flow.

Acetate is produced from the catabolism of carbohydrates, fatty acids, and, in nutritionally deficient states, amino acids. It reacts with oxaloacetate in the mitochondrion, after esterification with coenzyme A (also known as acetyl-CoA), to form citrate in the Krebs or tricarboxylic acid (TCA) cycle (see Fig. 2.1). Here, catabolic reactions result in CO_2 release and the transfer of hydrogen ions (protons) and their associated electrons to the mitochondrial electron transport chain, which then flow down the energy gradient of the electron transport chain, transferring energy to resynthesize ATP from adenosine diphosphate (ADP) and inorganic phosphate (i.e., oxidative phosphorylation). At the end of the electron transport chain, cytochrome oxidase catalyzes the reaction of each pair of protons and electrons with an atom of oxygen to form a molecule of water. For each transfer of a pair of protons and electrons, sufficient energy is released to form either two or three ATP molecules—three if the electron transport process begins at nicotinamide adenine dinucleotide (NAD^+), but only two if it begins at flavin adenine dinucleotide (FAD) (see Fig. 2.1).

Six ATP molecules are gained during the catabolism of glucose to pyruvate if the reduced nicotinamide adenine dinucleotide ($[NADH + H^+]$) in the cytosol, formed during glycolysis, is reoxidized by the proton shuttle and FAD (see pathway A of Fig. 2.1).[83] Of the six ATP molecules regenerated from glucose (seven from glycogen) by this mechanism, two are formed in the cytosol by the Embden-Meyerhof (glycolytic) pathway and four in

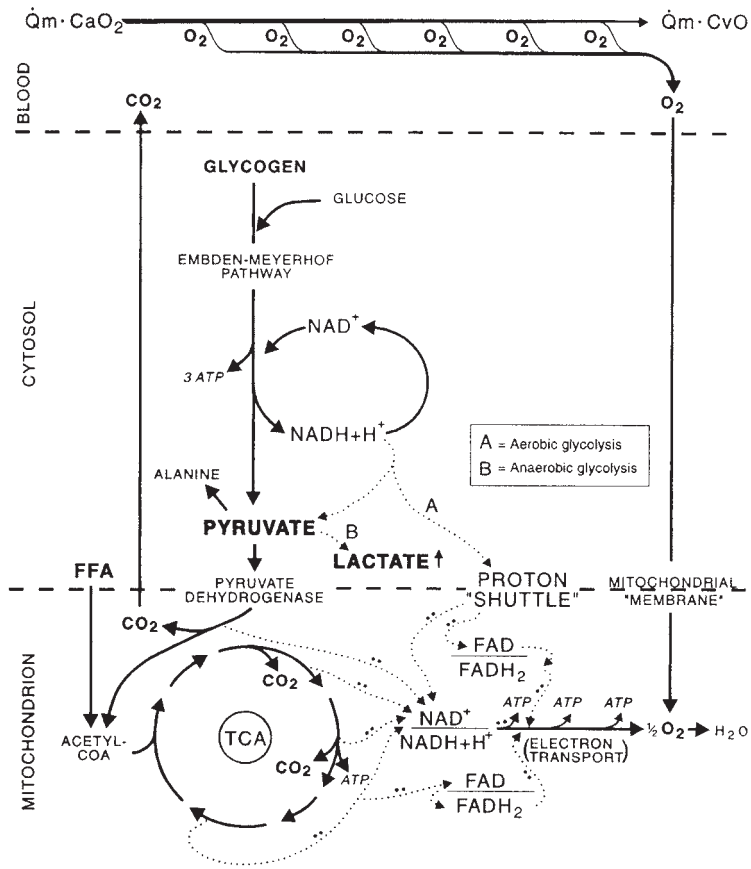

FIGURE 2.1. Scheme of the major biochemical pathways for production of adenosine triphosphate (ATP). The transfer of H^+ and electrons to O_2 by the electron transport chain in the mitochondrion and the "shuttle" of protons from the cytosol to the mitochondrion (pathway A) are the essential components of aerobic glycolysis. This allows the efficient use of carbohydrate substrate in regenerating ATP to replace that consumed by muscle contraction. Also illustrated is the important O_2 flow from the blood to the mitochondrion, without which the aerobic energy generating mechanisms within the mitochondrion would come to a halt. At the muscle sites of inadequate O_2 flow to mitochondria, pathway B serves to reoxidize NADH + H^+ to NAD^+. Pyruvate is converted to lactate (highly dissociated lactic acid at the cell pH), as NADH + H^+/NAD^+ increases in the cytosol.

the mitochondrion during the coupled reoxidation of cytosolic NADH + H^+ by the mitochondrion, via the mitochondrial membrane proton shuttle and the cytochrome electron transport chain.[83] The shuttle accepts hydrogen ions from the cytosolic [NADH + H^+] and transfers them to mitochondrial coenzymes, NAD^+ or FAD, as illustrated in Figure 2.1. This method of regenerating oxidized NAD^+ in the cytosol maintains the cytosolic redox state and enables glycolysis to continue. Because O_2 is the ultimate recipient of the protons that are generated by glycolysis and transported into the mitochondria, this glycolysis is aerobic (see pathway A in Fig. 2.1).

The formation of acetyl-CoA from pyruvate and its subsequent entry into the TCA cycle yields a total of five reduced mitochondrial NAD molecules (i.e., [NADH + H^+]). Because the reoxidation of each [NADH + H^+] by the electron transport chain yields 3 ATP molecules, there is a net gain of 15 ATP. However, 2 molecules of acetyl-CoA are formed from each glucose molecule, so the total gain is 30 ATP from these reactions. When added to the 2 ATP gained from glycolysis and the 4 others obtained from reoxidation of cytosolic [NADH + H^+] by the proton shuttle with the subsequent transfer of its protons and electrons to oxygen (see Fig. 2.1), the total gain in ATP from the complete oxidation of glucose is 36. However, glycogen is the major carbohydrate source in the normally nourished person, so an additional ~P is obtained because when a glycosyl unit combines with inorganic phosphate, it becomes ~P. Thus, there is a net yield of 37 ATP molecules from the aerobic oxidation of each glycosyl unit. Because 6 molecules of O_2 are used for glucose (glycosyl) oxidation and 36 high-energy phosphate bonds are formed, the ratio of ~P to O_2 is 6 for glucose (6.18 for glycogen). Six molecules of CO_2 and H_2O are catabolic end products of these reactions.

Under conditions in which the mitochondrial proton shuttles fail to reoxidize the [NADH + H^+] generated by glycolysis at a rate sufficient to keep cytosolic [NADH + H^+]/NAD^+ normal (Fig. 2.1), the redox state of the cytosol is lowered. Because [NADH + H^+] accumulates in the cytosol at the expense of NAD^+, glycolysis would slow if it were not for an alternate pathway capable of reoxidizing cytosolic [NADH + H^+]. When [NADH + H^+] accumulates, pyruvate can reoxidize the [NADH + H^+] back to NAD^+. However, by its acceptance of the two protons, pyruvate is reduced to lactate (see pathway B in Fig. 2.1). Thus, pyruvate oxidation of [NADH + H^+] results in lactate accumulation. Because the breakdown of glucose or glycosyl to lactate occurs without use of oxygen, it is termed *anaerobic glycolysis*. The substrate price for the production of energy from this reaction is expensive compared with the complete oxidation of glycogen to CO_2 and H_2O. The net gain in ATP is only 3 from each glycosyl unit instead of 37. For the same work rate, therefore, this pathway causes

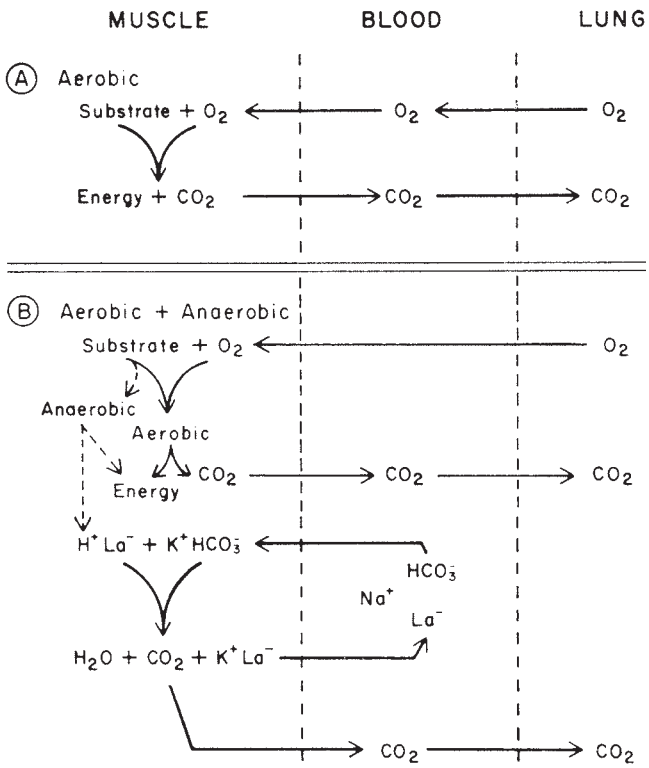

FIGURE 2.2. Gas exchange during aerobic **(A)** and aerobic plus anaerobic **(B)** exercise. The acid–base consequence of the latter is a net increase in cell lactic acid production. The buffering of the accumulating lactic acid takes place in the cell at the site of formation by bicarbonate. The latter mechanism will increase the CO_2 production of the cell by approximately 22 mL per mEq of bicarbonate buffering lactic acid. The increase in cell lactate and decrease in cell bicarbonate will result in chemical concentration gradients, causing lactate to be transported out of and bicarbonate to be transported into the cell.

glycogen (and glucose) to be used at a considerably faster rate than when the production of ~P is totally aerobic.[35,60] Moreover, the two lactic acid molecules that accumulate when each glucose molecule or glycosyl unit undergoes anaerobic metabolism cause a disturbance in acid–base balance in the cell and blood (Fig. 2.2). That the turn-on of anaerobic ATP production does not signal the turn-off of aerobic ATP production deserves emphasis. Both aerobic and anaerobic mechanisms share in energy generation at high work rates, with the anaerobic mechanism providing an increasing proportion of energy as the work rate is increased.

Phosphocreatine Splitting Kinetics

Oxygen uptake ($\dot{V}O_2$) during exercise is inextricably linked to increased rates of high-energy phosphate utilization. It is the major source of resynthesis of ATP, which is used to fuel muscular contraction through the process of oxidative phosphorylation. Phosphocreatine (PCr), with an intracellular concentration some five times greater than that of ATP, also serves as a mediator of ATP resynthesis through the creatine kinase reaction; that is,

$$PCr + ADP + H^+ \leftrightarrow Cr + ATP$$

Note that the breakdown of PCr produces an alkalinizing reaction.

Kushmerick and Conley called PCr a "chemical capacitor" for ATP.[81] The decrease in PCr concentration contributes to the O_2 deficit from the start of exercise, with its contribution to the O_2 deficit being proportionally greater the slower the time course of the $\dot{V}O_2$ increase. In fact, for moderate-intensity exercise, the sum of the utilization of PCr and O_2 stores is sufficient to account for the entire O_2 deficit. At higher work rates, however, anaerobic energy transfer from lactate production supplements these stored resources.

In addition to serving as what has been termed an energy buffer, PCr is also thought to play an important role in the control of oxidative phosphorylation, likely in its link to local ADP:

$$[ADP] = ([ATP][Cr])/([PCr]\ [H^+]\ Keq)$$

where Keq is the equilibrium constant of the creatine kinase reaction. ADP consequently increases as PCr decreases; thus, the ADP increase and/or PCr decrease might be the signal that triggers mitochondrial O_2 uptake.[169] In fact, the time course of the change in [PCr], measured by nuclear magnetic resonance spectroscopy, has been shown to be indistinguishable from that of $\dot{V}O_2$ (and, by extension, cellular O_2 consumption) in exercising humans.[113] These reactions are reversed in early recovery and constitute part of the repayment of the O_2 debt.

Substrate Utilization and Regulation

At this point, several terms need to be clarified for precision and to avoid possible confusion (see Fig. 1.3). The symbol $\dot{V}O_2$ indicates O_2 uptake by the lungs per minute. It is distinguished from O_2 consumption by the cells, which is symbolized by $\dot{Q}O_2$. The symbol $\dot{V}CO_2$ indicates CO_2 output by the lungs per minute, distinguished from CO_2 production by the cells, symbolized by $\dot{Q}CO_2$. Thus, the substrate mixture undergoing oxidation is characterized by the net rates of CO_2 yield or production ($\dot{Q}CO_2$) and oxygen utilization or consumption ($\dot{Q}O_2$). The ratio $\dot{V}CO_2/\dot{V}O_2$ as measured at the airway (i.e., the gas exchange ratio, R) reflects $\dot{Q}CO_2/\dot{Q}O_2$, the metabolic respiratory quotient (RQ), *only* when there is a steady state in $\dot{V}CO_2$ and $\dot{V}O_2$; that is, when CO_2 is not being added to or being removed from the body, CO_2 stores and the O_2 stores are constant. Thus, the new $\dot{V}CO_2$ and $\dot{V}O_2$ are equal to the new $\dot{Q}CO_2$ and $\dot{Q}O_2$, respectively (i.e., when $\dot{Q}CO_2 = \dot{V}CO_2$ and $\dot{Q}O_2 = \dot{V}O_2$).

During acute hyperventilation (resulting from, e.g., acute hypoxia, pain, or anxiety, or of volitional origin), considerably more CO_2 is unloaded from the body CO_2 stores than O_2 is loaded into the O_2 stores. This is because hemoglobin, at sea level, is almost completely saturated with O_2 at the end of the pulmonary capillaries and the physical solubility of O_2 in blood is low; on the other hand, appreciable amounts of CO_2 can be unloaded from blood and tissue stores as alveolar ventilation is increased and Pa_{CO_2} is reduced. Thus, with acute hyperventilation, R will exceed the metabolic RQ until a steady state (i.e., CO_2 output equals CO_2 production) is again attained at the new level of ventilation. Similarly, during the acute metabolic acidosis of exercise, "extra" CO_2 is evolved when HCO_3^- buffers lactic acid (see Fig. 2.2). This will also result in R exceeding RQ until a new steady state in CO_2 stores is attained (i.e., the CO_2 pool size is again constant, although depleted, and CO_2 output equals production), at which time R again equals RQ. Differences between R and RQ will also occur during acute hypoventilation and recovery from metabolic acidosis, but in the opposite direction.

As seen in the following equations, carbohydrate (e.g., glycogen or glucose) is oxidized with RQ equal to 1.0 (i.e., six CO_2 molecules produced and six O_2 molecules consumed) and, ideally, has a ~P:O_2 of 6.0 or 6.18, depending on whether glucose or glycogen is the substrate:

$$C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O + 36 \text{ or } 37\ ATP \quad (1)$$

Lipid (e.g., palmitate) is oxidized with RQ equal to 0.71 (i.e., 16 CO_2 produced to 23 O_2 consumed) and has a ~P:O_2 of 5.65 (i.e., 130 ATP/23 O_2):

$$C_{16}H_{32}O_2 + 23\ O_2 \rightarrow 16\ CO_2 + 16\ H_2O + 130\ ATP \quad (2)$$

Intermediate steady-state RQ values reflect different proportions of carbohydrate and fat being utilized in the bioenergetic, metabolic process (Fig. 2.3). For storage economy, fat is the more efficient energy; however, for economy of O_2 utilization, carbohydrate is the more efficient substrate, supplying 6% to 8% more ATP per mole of O_2 with carbohydrate as compared to fat.

When a steady state of gas exchange exists, R provides an accurate reflection of RQ. During exercise, the muscle RQ can be estimated from the increase in $\dot{V}_{CO_2}$ relative to the increase in $\dot{V}_{O_2}$over the range of moderate work rates. These gas exchange measurements suggest that the muscle substrate RQ during exercise is approximately 0.95, when a normal diet is ingested.[10,32,34] This is in close agreement with the muscle substrate RQ in normal humans found by Bergstrom and associates based on the rate of muscle glycogen consumption during exercise determined from repeated muscle biopsies.[14] Thus, to economize on O_2 transport, a greater proportion of carbohydrate than of fatty acids is used for energy during muscular work as compared with the resting state.[127]

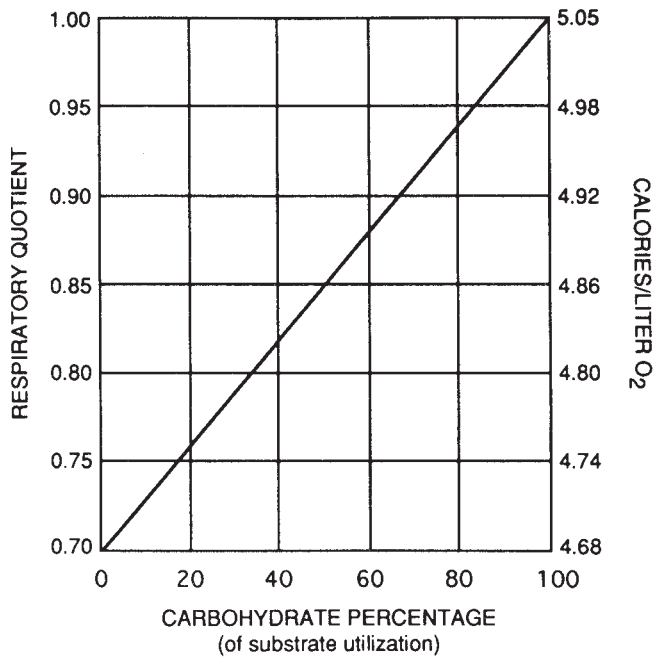

FIGURE 2.3. The percentage of carbohydrate substrate in the diet estimated from the respiratory quotient measurement. The calories of energy obtained per liter of oxygen consumed for each combination is given on the right ordinate. (From Lusk G. *Science of Nutrition.* New York, NY: Johnson Reprint; 1976, with permission.)

Because muscle RQ is high relative to that of most other organs (with the exception of the nervous system), the total body RQ increases from a resting value of approximately 0.8 (on an average Western diet) toward approximately 0.95 during moderate exercise, depending on the exercise metabolic rate (Fig. 2.4). An RQ of 0.95 indicates that about 84% of the substrate during exercise is derived from carbohydrate (see Fig. 2.3). Although the fuel mixture for the total body derives proportionally more from carbohydrate than from lipid stores during exercise as work rate increases (see Fig. 2.4), RQ decreases slowly over time during prolonged constant-load exercise (Fig. 2.5). This reflects a decrease in the proportional utilization of carbohydrate associated with a reduction in muscle glycogen stores. When muscle glycogen becomes depleted, the exercising subject senses exhaustion.[111] Acute ingestion of glucose may allow the work to continue.[124]

The rate of decrease in muscle glycogen during exercise can be slowed by raising blood glucose levels with a continued infusion of glucose.[3] The importance of muscle glycogen in work tolerance is well described by the experiments of Bergstrom et al.,[14] who demonstrated a

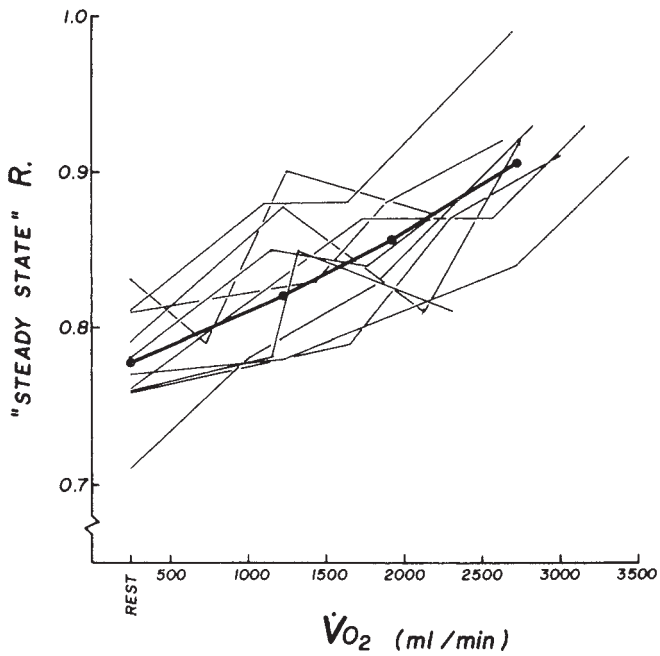

FIGURE 2.4. The steady-state R (RQ) at various levels of exercise for the whole body determined as the ratio of steady-state $\dot{V}CO_2$ to $\dot{V}O_2$ for the levels of exercise indicated on the *x*-axis for 10 subjects. The *heavy line* is the average response.

high positive correlation between the tolerable duration of high-intensity work and the muscle glycogen content before exercise.

Physical fitness, in the sense of the capacity for sustained activity, affects the substrate utilization pattern. A fitter subject uses a greater proportion of fatty acids for energy than an unfit one for submaximal work.[63] This mechanism conserves glycogen, allowing more work to be performed before glycogen depletion and consequent exhaustion. The specific regulation of different substrates is considered in the following sections.

Carbohydrates

Skeletal muscle in humans contains, on average, 80 to 100 mmol (15 to 18 g) glucose per kilogram of wet weight stored as glycogen. For a 70-kg man, this amounts to approximately 400 g of muscle glycogen.[14] However, a contracting muscle can draw only on its own glycogen reserves and not on the pools in noncontracting muscles.

Normally, approximately 4 to 5 g of glucose are available in the blood (100 mg/100 mL). Although muscle uptake of blood glucose increases considerably during exercise, the blood concentration does not fall because of an increased rate of glucose release from the liver. The liver represents a highly labile glycogen reserve in the range of 50 to 90 g. This glycogen is broken down into glucose by glycogenolysis and released into the blood. Glucose can also be produced in the liver (gluconeogenesis) from lactate, pyruvate, glycerol, and alanine precursors. The rate of glucose release from the liver into the circulation depends on both the blood glucose concentration and a complex interaction of hormones such as insulin, glucagon, and the catecholamines epinephrine and norepinephrine.[138,139] As exercise intensity and duration increase, the circulating levels of catecholamines and glucagon increase, thereby maintaining the level of blood glucose despite its increased utilization by the exercising muscles. These regulatory processes maintain physiologically adequate concentrations of glucose, except when muscle and liver glycogen stores become greatly depleted.

Lipids

Skeletal muscles have access to their own intramuscular store of lipids, averaging 20 g of triglycerides per kilogram of wet weight. This source accounts for a considerable proportion of the total energy required by the muscles, depending on the duration of exercise and the rate of muscle glycogen depletion.

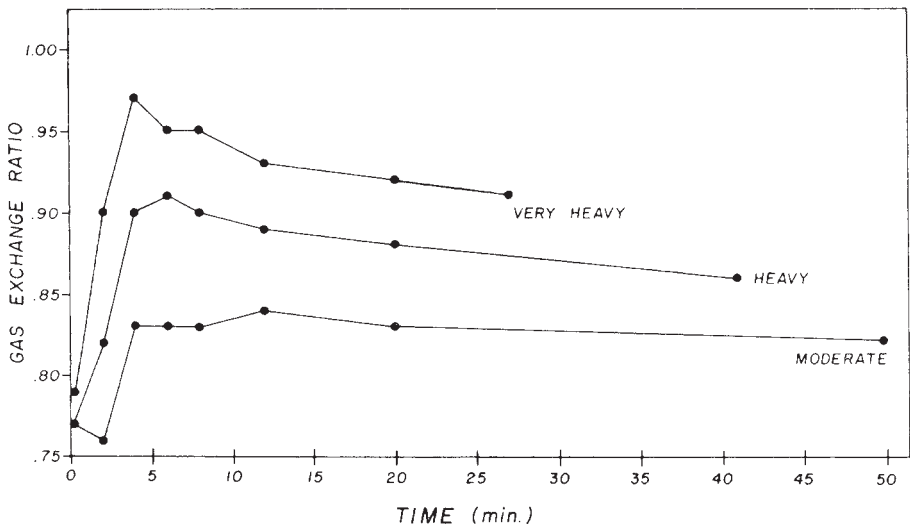

FIGURE 2.5. Effect of exercise duration on the gas exchange ratio (R) for constant work rate exercise of moderate, heavy, and very heavy work intensity. Note that the R is higher for the higher work intensities, but slowly declines with time after the initial increase. Results are those for a single healthy subject. The R is higher with greater exercise intensity, indicating a higher carbohydrate to fat ratio at higher work rates. The slow decline in R likely results from a slow depletion of the muscle carbohydrate stores.

Extramuscular lipid sources are also used during exercise. These derive from adipose tissue where triglycerides undergo hydrolysis to glycerol and free fatty acids (mainly palmitic, stearic, oleic, and linoleic acids). The fatty acids are transported in the blood, bound predominantly to albumin. The store of extramuscular lipid is large. In a 70-kg man, fat accounts for approximately 15 kg of triglycerides, which is equivalent to about 135,000 Kcal of energy.

The sympathetic nervous system, along with catecholamines from the adrenal medulla, regulate adipose tissue lipolysis. Epinephrine and norepinephrine increase the local concentration of cyclic 3′,5′-AMP through activation of adenyl cyclase. This leads to increased rates of hydrolysis of the stored adipose tissue triglycerides. Other factors reduce the rate of adipose tissue lipolysis during exercise, including increased blood lactate and exogenous glucose loads.

The free fatty acids account for only a small proportion (usually less than 5%) of the total plasma fatty acid pool; the remainder are triglycerides. Resting plasma free fatty acid concentrations are approximately 0.5 mmol/L, increasing during exercise to approximately 2 mmol/L. The turnover rate of the plasma free fatty acid pool is high, with a half-time of 2 to 3 minutes at rest and less during exercise. As a consequence, the flux of free fatty acids to the exercising muscle (i.e., plasma flow × plasma free fatty acid concentration) is an important determinant of skeletal muscle uptake.

The plasma concentration of free fatty acids does not increase—and may even decrease slightly—with physical training. Therefore, the increased proportional contribution of free fatty acid oxidation to exercise energetics, when measured at a specific work rate after training, may reflect increased utilization from intramuscular sources. Adipose tissue lipolysis does not appear to be enhanced by training.

Amino Acids

During exercise, the rate of release of intramuscular alanine increases appreciably, but with little or no change in other amino acids.[106] The arterial alanine concentration increases as much as twofold during severe exercise.[134] The source of the alanine released from muscle is predominantly from the transamination of pyruvate (derived from increased rates of carbohydrate metabolism). The amino groups are derived from the deamination of inosine monophosphate during purine nucleotide metabolism and the branch-chain amino acids (valine, leucine, and isoleucine).

A highly linear relationship exists between the plasma concentrations of alanine and pyruvate at rest and during exercise. A decreased muscle release of alanine, associated with the decreased output of pyruvate,[135] is observed in phosphorylase-deficient muscle (McArdle syndrome). The alanine formed by transamination in muscle is transported in the blood to the liver, where it serves as a precursor for gluconeogenesis. Thus, an alanine–glucose cycle is established between muscle and liver, with the carbon skeleton of alanine supporting hepatic glucose synthesis.

OXYGEN COST OF WORK

The oxygen cost of performing work depends on the work rate. Figure 2.6 shows the time course of oxygen uptake ($\dot{V}O_2$) from unloaded cycling for various levels of cycle ergometer exercise in a normal individual. Note that, in this individual, a steady state is reached by 3 minutes up to a work rate of 150 W. At higher work rates, $\dot{V}O_2$ continued to increase above the 3-minute value, and the subject was unable to continue the exercise task.[162,166] The maximum $\dot{V}O_2$ for each work rate above 200 W was the same, thereby identifying the subject's $\dot{V}O_2$max. Note that the earlier the $\dot{V}O_2$max is reached, the higher the work rate, thus signifying that the subject reached the level of fatigue earlier (i.e., characterizing the subject's power–duration relationship at this work intensity). The subject cannot sustain exercise at $\dot{V}O_2$max. The $\dot{V}O_2$ kinetic profiles shown in Figure 2.6 are typical of all subjects, but the work rate at which the non–steady-state pattern of $\dot{V}O_2$ is seen differs depending on the subject's fitness for aerobic work.

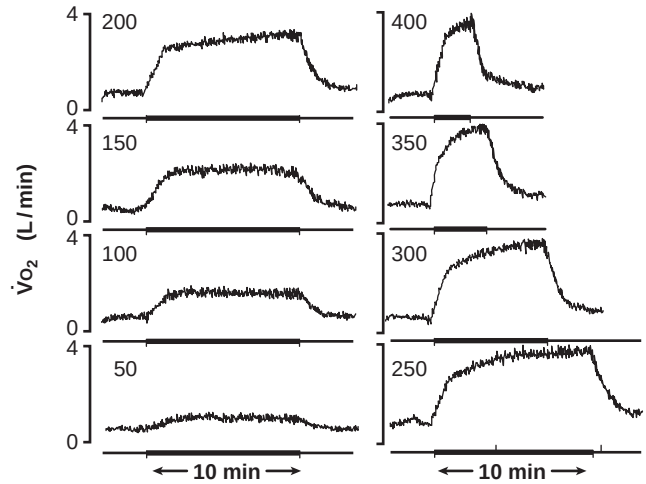

FIGURE 2.6. Breath-by-breath time course of oxygen uptake for eight levels of constant work rate cycle ergometer exercise, starting from unloaded cycling, for a normal male subject. The work rate (watts) for each study is shown in the respective panel. The *bar* on the *x*-axis indicates the period of the imposed work rate. The $\dot{V}O_2$ asymptote (steady state) is significantly delayed for work above the anaerobic threshold. (From Whipp BJ, Mahler M. Dynamics of pulmonary gas exchange during exercise. In: West JB, ed. *Pulmonary Gas Exchange*. New York, NY: Academic Press, 1980:33–96, with permission.)

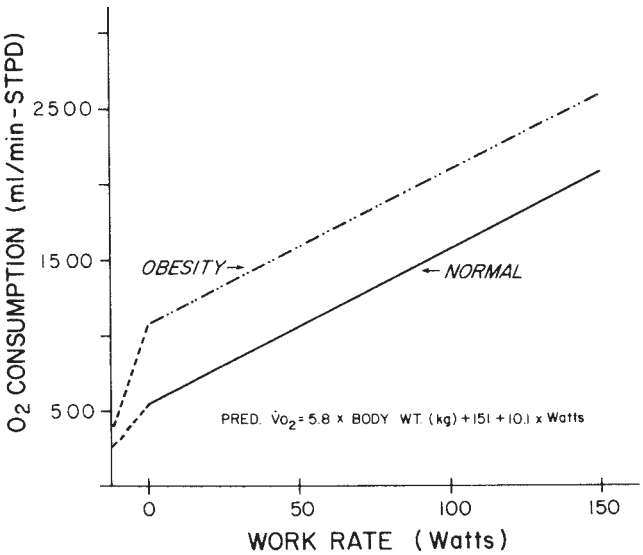

FIGURE 2.7. The effect of work rate on steady-state oxygen consumption during cycle ergometer exercise. The oxygen consumption response in normal subjects is quite predictable for cycle ergometer work regardless of age, gender, or training. The predicting equation is given in the figure. In obese subjects, the oxygen requirement to perform work is displaced upward, with the displacement dependent on body weight. (From Wasserman K, Whipp BJ. Exercise physiology in health and disease. *Am Rev Respir Dis.* 1975;112:219–249, with permission.)

When plotting the steady-state $\dot{V}O_2$ values for those cycle ergometer work rates in which a steady state is achieved, such as shown for 50, 100, and 150 W in Figure 2.6, a linear relationship between $\dot{V}O_2$ and work rate is obtained (Fig. 2.7). The slope of this relationship is approximately the same for all normal people (approximately 10 mL/min/W), although it appears to be slightly steeper (approximately 11 mL/min/kg) in highly fit cyclists.[110] Therefore, work efficiency in humans is relatively fixed for a given work task. Although the slope of the relationship between steady-state $\dot{V}O_2$ and work rate is not perceptibly affected by age or sex, the position of the relationship depends on body weight.

On the cycle ergometer, obese subjects exhibit an upward displacement of approximately 5.8 mL/min/kg of body weight,[150] which reflects the added work rate generated as a result of moving the heavier lower extremities. The effect of body weight on $\dot{V}O_2$ is more pronounced on the treadmill because an even greater work rate must be done to support the movement of the entire body through space.

Work Efficiency and Steady-State $\dot{V}O_2$

Cycle ergometer work rate and the steady-state $\dot{V}O_2$ measurement are commonly used interchangeably when describing the level of exercise being performed, because work efficiency or the increase in work rate (ΔWR) as related to the energy equivalent of the increase in $\dot{V}O_2$ required to perform the work ($\Delta\dot{V}O_2$) varies only slightly from one individual to another.[6] Trained and untrained individuals, regardless of age and sex, all have similar work efficiencies. This similarity reflects the basic biochemical energy-yielding reactions needed for muscle contraction. However, it is important to recognize that the $\dot{V}O_2$ of the "unloaded" ergometer can vary considerably from one subject to another because of differences in subject size and the actual work rate of the "unloaded" cycling. Thus, $\Delta\dot{V}O_2/\Delta WR$ is much more uniform among subjects than $\dot{V}O_2/WR$.

Care must be taken not to confuse changes in skill or motor efficiency due to practice with the assessment of work efficiency. To measure work efficiency, relatively simple tasks must be employed that do not depend on technique and for which the work output can be measured (e.g., cycling). To calculate muscle work efficiency, the caloric equivalent of the steady-state $\dot{V}O_2$ (4.98 Cal/L $\dot{V}O_2$ at RQ = 0.95, see Fig. 2.3) and the external power (0.014 Cal/min/W) for at least two measured work rates must be known. For lower-extremity cycle ergometer work, normal subjects have an efficiency of approximately 28%.[150,165]

$\dot{V}O_2$ Non–Steady State

The continued slow increase in $\dot{V}O_2$ observed after 3 minutes during constant work rate exercise in healthy young subjects is only seen for work rates that are accompanied by a lactic acidosis.[114,162,166] The rate of increase in $\dot{V}O_2$ in response to constant work rate exercise for 3 to 6 minutes correlates with the increase in blood lactate,[76,114,166,176] as discussed in "Gas Exchange Kinetics" later in this chapter. At least six mechanisms may contribute to the slow increase in $\dot{V}O_2$ after 3 minutes of exercise:

1. Increase in $\dot{V}O_2$ needed to satisfy the increased work of the muscles of respiration and the heart at high ventilatory and cardiac output responses
2. Calling into play additional groups of muscles (such as more forceful pulling on the handlebars)
3. Acidemia facilitating O_2 unloading from hemoglobin by shifting the oxyhemoglobin dissociation curve downward and rightward for a given P_{O_2}
4. Progressive vasodilation to the local muscle units by metabolic vasodilators (e.g., $\uparrow[H^+]$, $\uparrow P_{CO_2}$, $\downarrow P_{O_2}$, sheer stress), thereby increasing O_2 flow and O_2 consumption at the O_2-deficient sites
5. The O_2 cost of converting lactate to glycogen in the liver as the lactate concentration rises, which must also contribute to the increase in $\dot{V}O_2$, but its magnitude is quite small compared to the rate of $\dot{V}O_2$ increase during the slow phase[168]
6. And predominantly, reduced muscular efficiency during heavy work by recruiting more low-efficiency fast-twitch muscle fibers.

Power-Duration Curve and Critical Power

The power-duration curve describes the time for which high-intensity, constant-load exercise may be sustained to the limit of tolerance (t_{LIM}). This relationship has been demonstrated to be hyperbolic for work rates that result in $\dot{V}O_2$max being attained (Fig. 2.8A). This provides a power asymptote at what is termed the *critical power* (CP)—a parameter that correlates highly with the subject's aerobic capacity and which increases with endurance training in concert with the lactate threshold and $\dot{V}O_2$max. The curvature constant of the hyperbola, *W′*, is a parameter of exercise tolerance that is mathematically equivalent to a constant amount of work (i.e., the product of P and t_{LIM}) that can be performed above CP.[97,104] When P is plotted as a function of the reciprocal of time ($1/t_{LIM}$), the relationship is highly linear (Fig. 2.8B) with a slope indicative of *W′*. CP presumably partitions the supralactate threshold exercise intensity into its heavy and very heavy intensity domains.[159] Exercise training that increases the endurance time for the work rate domain above the CP would affect *W′* and the CP; it can be used to evaluate the benefit of exercise training or therapy.

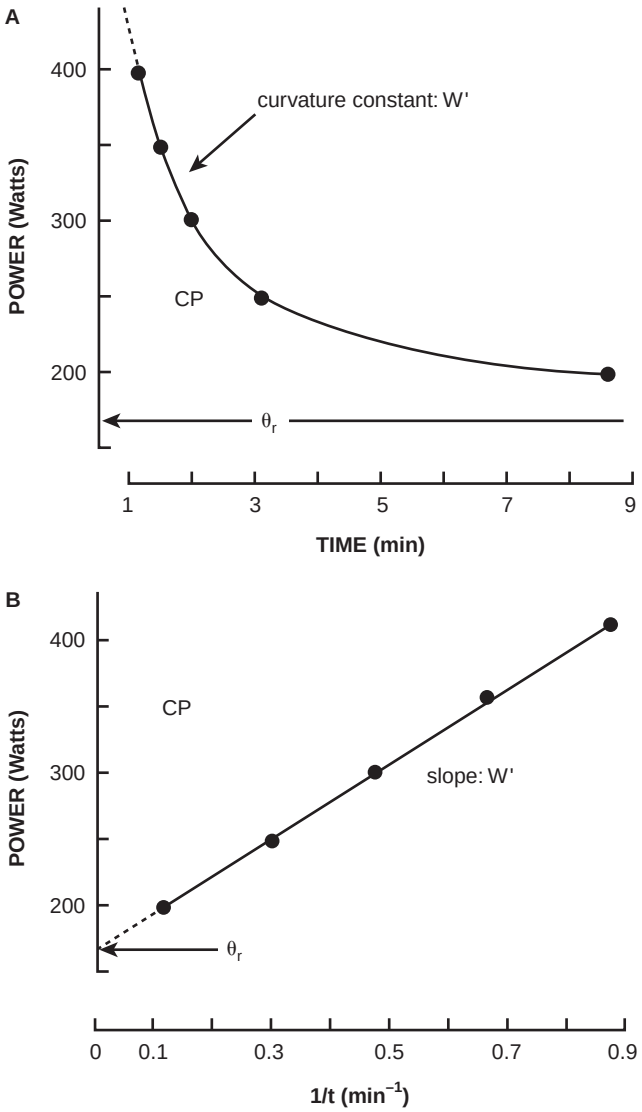

FIGURE 2.8. **A:** The hyperbolic relationship between power and its tolerable duration for very heavy intensity exercise. The power asymptote (*horizontal line*) provides an estimation of the subject's critical power (CP), with a curvature constant termed W′. **B:** The linearized relationship between power and the inverse of its tolerable duration. The subject's CP is determined from the linear extrapolation, as shown. W′ provided by the slope of this relationship. (Modified from Fukuba Y, Whipp, BJ. A metabolic limit on the ability to make up for lost time in endurance events. *J Appl Physiol.* 1999;87:853–861.)

LACTATE INCREASE

Lactate Increase as Related to Work Rate

Figure 2.9 shows the arterial blood lactate concentration as related to $\dot{V}O_2$ in three groups of subjects performing progressively increasing cycle ergometer work: normal subjects who are relatively active, sedentary

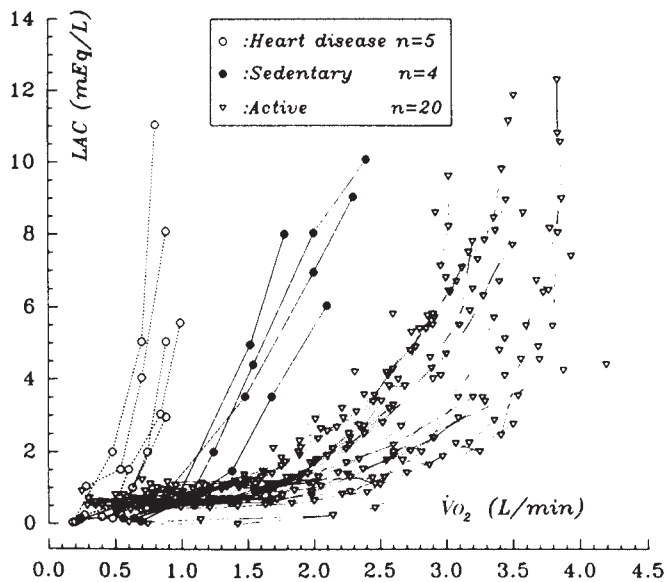

FIGURE 2.9. Pattern of increase in arterial lactate in active and sedentary healthy subjects and patients with heart disease as related to increasing exercise oxygen uptake $\dot{V}O_2$. Lactate (LAC) concentration rises from approximately the same resting value to approximately the same concentration at maximal exercise in each of the three groups. The fitter the subject for aerobic work, the higher the $\dot{V}O_2$ before lactate starts to increase significantly above resting levels. (Modified from Wasserman K. Coupling of external to cellular respiration during exercise: the wisdom of the body revisited. *Am J Physiol.* 1994;266: E519–E539.)

normal subjects, and patients with heart disease. All show similar resting and low-level exercise lactate concentrations. The pattern of lactate increase is the same for each group, but the $\dot{V}O_2$ at which the lactate starts to increase differs. Lactate does not start to increase in subjects who are relatively young and physically active until $\dot{V}O_2$ is increased to as much as 10 times the resting metabolic rate. In contrast, the $\dot{V}O_2$ at which lactate starts to increase in sedentary subjects is about four times the resting level (equivalent to the $\dot{V}O_2$ required for adults to walk at a normal pace). In cardiac patients with a low, symptom-limited maximum $\dot{V}O_2$, arterial lactate increases at exceedingly low exercise levels, perhaps less than twice that of the resting metabolic rate, as shown in Figure 2.9.

The $\dot{V}O_2$ at which lactate starts to increase in normal subjects is, on average, about 50% to 60% of their $\dot{V}O_2$max, but with a range extending from 40% to more than 80%. It is higher in aerobically fit subjects. The lactate threshold (*LT*) and $\dot{V}O_2$max increase with endurance training. As a person ages, the $\dot{V}O_2$ at the *LT* becomes a higher fraction of $\dot{V}O_2$max because $\dot{V}O_2$max decreases at a proportionately faster rate than the *LT*.

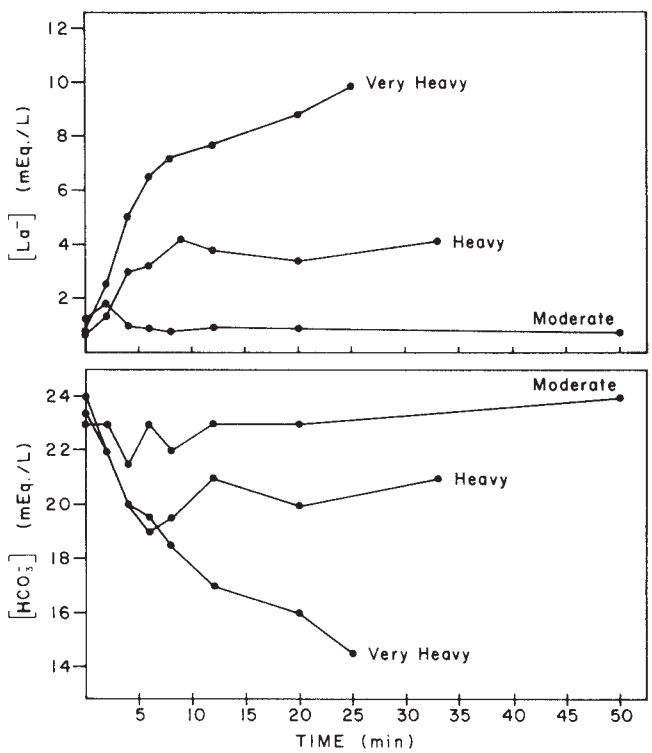

FIGURE 2.10. Arterial lactate increase and bicarbonate decrease with time for moderate, heavy, and very heavy exercise intensities for a normal subject. Bicarbonate changes in an opposite direction to lactate, in a quantitatively similar manner. Although the target exercise duration was 50 minutes for each work rate, the endurance time was reduced for the heavy and very heavy work rates.

Lactate Increase as Related to Time

Work rate or power output is an absolute quantity of work performed per unit of time. Although a given work rate may be stressful for one individual and thus cause early fatigue, it may not be a significant physical stress for a more fit individual. Therefore, adjectives such as *moderate, heavy,* and *very heavy* are used to describe the degree of physical stress based on the pattern of arterial lactate change.[148] The magnitude and pattern of arterial lactate increase for a given work rate closely reflect the fitness of an individual for endurance (aerobic) exercise.[140]

For constant-load cycle ergometer exercise, three patterns of arterial blood lactate concentration increase are observed (Fig. 2.10).[148] The first pattern is one in which either no increase in lactate is observed or lactate transiently rises and then returns to its resting value as $\dot{V}O_2$ reaches a steady state. This is defined as *moderate work intensity* and implies that the work is not uncomfortable and hence can be sustained in a true steady state.

Heavy-intensity exercise is defined as a sustained but constant increase in arterial lactate resulting from a balance between increased rate of production by the exercising muscle and increased rate of utilization by the liver and other actively metabolizing organs, such as the heart. This work can only be sustained for a limited duration (Figs. 2.10 and 2.11) because a true metabolic steady state does not occur. The acid–base balance at this work intensity reflects a sustained metabolic acidosis.[152]

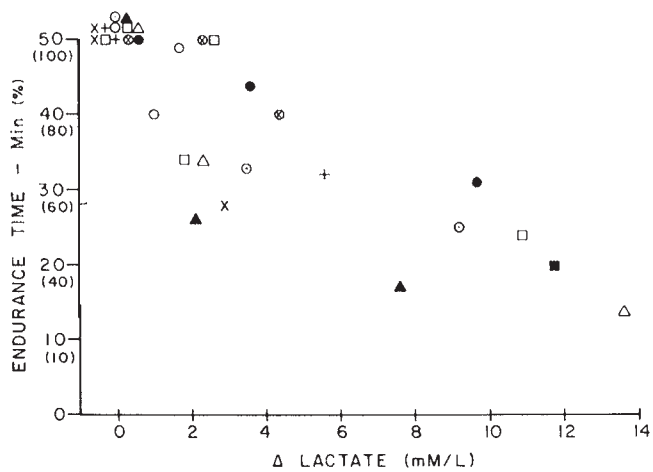

FIGURE 2.11. The endurance time as related to the increase in arterial lactate (above the preexercise resting value) during the last minute of constant work rate cycle ergometer exercise. Data are from 30 experiments on 10 male subjects, each studied at three work rates. The target exercise time for each work rate was 50 minutes. The target endurance time is reduced when lactate is increased. (From Wasserman K. The anaerobic threshold measurement to evaluate exercise performance. *Am Rev Respir Dis.* 1984;129:S35–S40, with permission.)

When arterial lactate continues to increase throughout the exercise to the point of fatigue (see Fig. 2.10), this is termed *very heavy exercise*. At these work rates, arterial lactate concentration in normal subjects typically continues to increase to levels as great as 10 mmol/L or more. Higher lactate causes earlier fatigue, whether arterial lactate is in the heavy or very heavy work intensity range (see Fig. 2.11).

Lactate Increase in Response to Increasing Work Rate

As illustrated in Figure 2.9, arterial lactate does not appreciably increase above resting values until a $\dot{V}O_2$ is reached above which lactate increases at a progressively steeper rate. To determine the best-fit mathematical model describing the $\dot{V}O_2$ at which lactate starts to increase, both continuous-exponential and threshold models were tested.[11,143] The purpose of this model testing was to better understand the physiological events that accompany the development of the highly reproducible lactic acidosis engendered by heavy exercise. To obtain a better picture of the systematic pattern of the change in arterial lactate with increasing $\dot{V}O_2$, the arterial blood lactate was plotted against the simultaneously measured $\dot{V}O_2$ after the $\dot{V}O_2$ scale was normalized to demonstrate a significant increase in arterial lactate for the 17 physically active, healthy young male subjects shown in Figure 2.12. In this plot, the data points are distributed with the same deviation relative to the average curve as they were distributed in the individual curves for each subject. Because lactate increases steeply with little increase in $\dot{V}O_2$ as $\dot{V}O_2$max is approached, the data were examined to address the question of model behavior for lactate increase during exercise (threshold or exponential), the analysis was restricted to the region of interest, from resting lactate to arterial lactate of 4.5 mmol/L.

As illustrated in Figure 2.12 (upper panel), a monoexponential model of lactate increase from rest as a function of $\dot{V}O_2$ does not describe the lactate data well. Lactate points fall above the model curve at the low $\dot{V}O_2$ values, whereas in the region of $\dot{V}O_2$ just below that at which lactate starts to rise (identified as the threshold in the threshold model), the points fall below the model curve. In contrast, the points distribute evenly around the two components of the threshold model (Fig. 2.12, lower panel). This threshold denotes the *LT*.

Neither the threshold nor the monoexponential models is a perfect fit for the lactate–$\dot{V}O_2$ relationship at all work levels. However, the data in the region of interest (i.e., below 4.5 mmol/L) clearly fit the threshold model better than the exponential model. Supporting the threshold model are numerous muscle biopsy studies that show that muscle lactate does not increase at work rates within the moderate-intensity domain.[31,65,72,75] The $\dot{V}O_2$ at which lactate begins to increase in arterial blood coincides with that of the muscle.[75]

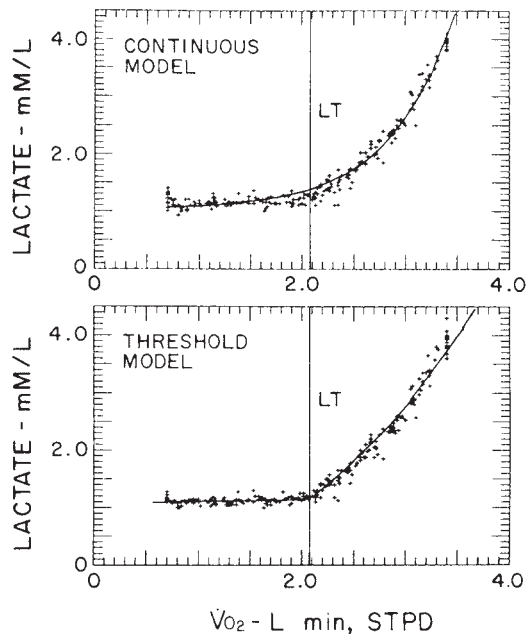

FIGURE 2.12. The threshold behavior of arterial lactate increase as related to $\dot{V}O_2$ in response to exercise. Data are arterial lactate measurements from 17 active healthy subjects (shown in Fig. 2.9). Points are plotted only up to a lactate level of 4.5 mmol/L (the region of interest in evaluating threshold versus a continuous exponential model). The *vertical solid line* shows the average threshold for the 17 subjects. The points for the individual subjects are plotted in the same relation to the threshold $\dot{V}O_2$ as existed in their individual plots. In the **upper panel**, the *solid curve* describes the continuous exponential model. Lactate values fall above the exponential model curve at the lowest $\dot{V}O_2$, whereas the lactate values are below the model curve in the region of the threshold. In contrast, the threshold model (*solid lines*, **lower panel**) is a better fit to the actual lactate measurements. (Details of the mathematical analysis for a smaller number of subjects are presented in Wasserman K, Beaver WL, Whipp BJ. Gas exchange theory and the lactic acidosis (anaerobic) threshold. *Circulation.* 1990; 81(suppl 1):II14–II30)

Mechanisms of Lactate Increase

Several mechanisms have the potential to yield increases in lactate production as $\dot{V}O_2$ increases during exercise, as described in the following sections.

Overload of the Tricarboxylic Acid Cycle

Lactate can accumulate in the muscle and blood during exercise if glycolysis proceeds at a rate faster than pyruvate can be utilized by the mitochondrial tricarboxylic acid cycle (see Fig. 2.1). This mechanism should cause lactate to increase as a result of and in proportion to pyruvate increase—that is, a mass action effect.

Sequential Recruitment of Fiber Types

Another mechanism proposed for the increase in lactate during exercise is the increased recruitment of type IIx muscle fibers above the *LT*.[62] These fibers contain high levels of glycogen. However, it has not been demonstrated that these fibers are activated at the *LT*. Furthermore, it would be necessary to demonstrate that type IIx fibers have a redox state with a higher NADH + H^+ to NAD^+ ratio and, therefore, higher lactate-to-pyruvate (L/P) ratio than types I or IIa fibers. Additionally, there is no evidence that activation of type IIx fiber types is influenced by changes in oxygenation, as is the case for arterial lactate concentration.

Change in Cytosolic Redox State due to Hypoxia Limiting the Mitochondrial Membrane Proton Shuttle

In the process of glycolysis (see Fig. 2.1), the oxidized form of cytosolic NAD^+ is converted into the reduced form (NADH + H^+). It is subsequently reoxidized back to NAD^+ by the mitochondrial membrane proton shuttle (see pathway A of Fig. 2.1). If, because of inadequate O_2 availability in the mitochondria to reoxidize cytosolic NADH + H^+ by the proton shuttle, the [NADH + H^+]/NAD^+ ratio increases (pathway B of Fig. 2.1). With this change in redox state of the muscle, reoxidation of cytosolic [NADH + H^+] can take place by pathway B of Figure 2.1 (pyruvate + [NADH + H^+] → lactate + NAD^+). This mechanism is operative when the oxygen required by the exercising muscles cannot be supplied at a sufficiently rapid rate to regenerate cytosolic NAD^+ by pathway A. Thus, the cell redox state is lowered (increased [NADH + H^+]/NAD^+), forcing an increase in the L/P ratio (Fig. 2.13).

Figure 2.13 shows a plot of the log–log transformation of arterial lactate, pyruvate, and L/P ratio as a function of $\dot{V}O_2$ in one normal subject who was representative of the average response of 10 healthy subjects.[142] Below the *LT*, lactate increased by a few tenths of a mmol/L as pyruvate increased, but the L/P ratio did not increase until the *LT* was reached. Pyruvate also increased steeply, but not until a $\dot{V}O_2$ was reached that was well above that of the *LT*. Also, the rate of increase in pyruvate was always slower than lactate. Consequently, the L/P ratio increased at the *LT* and continued to increase until $\dot{V}O_2$max. A similar phenomenon has been observed in the muscle cells of humans.[22] The increase in muscle L/P was accompanied by a reduction in the muscle energy charge, indicated by an increase in the ADP/ATP ratio.[22]

The increase in lactate with an increase in L/P ratio indicates that the increase in lactate during exercise is not simply a mass action phenomenon resulting from increased glycolysis. Rather, the lactate increase results from a shift in equilibrium between lactate and pyruvate as a result of change in the NADH + H^+/NAD^+ ratio (cytosolic redox state) (see Fig. 2.1). The conversion of pyruvate to lactate results in the reoxidation of cytosolic NADH + H^+, providing NAD^+ for continued glycolysis even under anaerobic conditions. Because no O_2 is used in the reoxidation of pathway B (see Fig. 2.1), this glycolysis is anaerobic. Simultaneously, reoxidation of cytosolic NADH + H^+ can take place aerobically, in better oxygenated contracting muscle cells, by pathway A; this is aerobic glycolysis (see Fig. 2.1). A reversal of the exercise-induced increase in arterial L/P is seen at the start of recovery (Fig. 2.14), which provides an important clue to the mechanism(s) of the lactic acidosis during the exercise. The exercise-induced rise in arterial lactate may continue into the recovery phase at a slowed rate for several minutes before it starts to decrease. Pyruvate concentration, on the other hand, actually increases more rapidly at the start of recovery (see Fig. 2.14, middle panel). Thus, as soon as exercise stops (and the O_2 requirement decreases), the L/P ratio reverses, supporting the evidence obtained during exercise that the exercise-induced lactate increase is not simply a mass action effect consequent to pyruvate increase. A reversal in L/P ratio, with lactate decreasing and pyruvate increasing, takes place in the muscle at the start of recovery.[142]

In summary, it is difficult to attribute the increase in lactate with an increase in L/P ratio, as seen with heavy exercise, solely to accelerated glycolysis, inadequate tricarboxylic acid cycle enzymes, or changes in contracting muscle fiber type. Rather, the experimental studies support the concept that the major mechanism accounting for the lactate increase at the *LT* is the lowering of

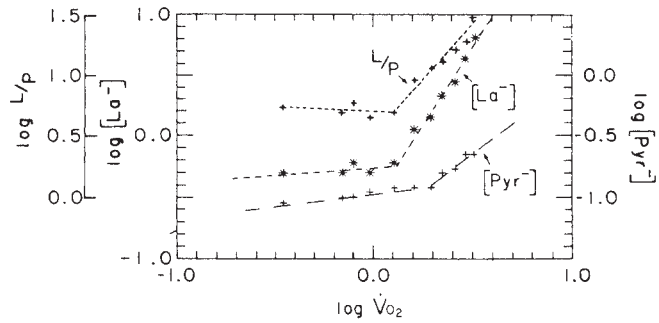

FIGURE 2.13. Log lactate (La^-), log pyruvate (Pyr^-), and log lactate-to-pyruvate (L/P) ratio plotted against log $\dot{V}O_2$. The log–log transform of the lactate-$\dot{V}O_2$ and pyruvate-$\dot{V}O_2$ relationships allows easy detection of the lactate and pyruvate inflection points. The pyruvate inflection point is at a higher $\dot{V}O_2$ than the lactate inflection point. Because the pre-threshold pyruvate slope is the same as the lactate slope, the L/P ratio does not increase until the lactate inflection point. (From Wasserman K, Beaver WL, Davis JA, et al. Lactate, pyruvate, and lactate to pyruvate ratio during exercise and recovery. *J Appl Physiol.* 1985;59:935–940, with permission.)

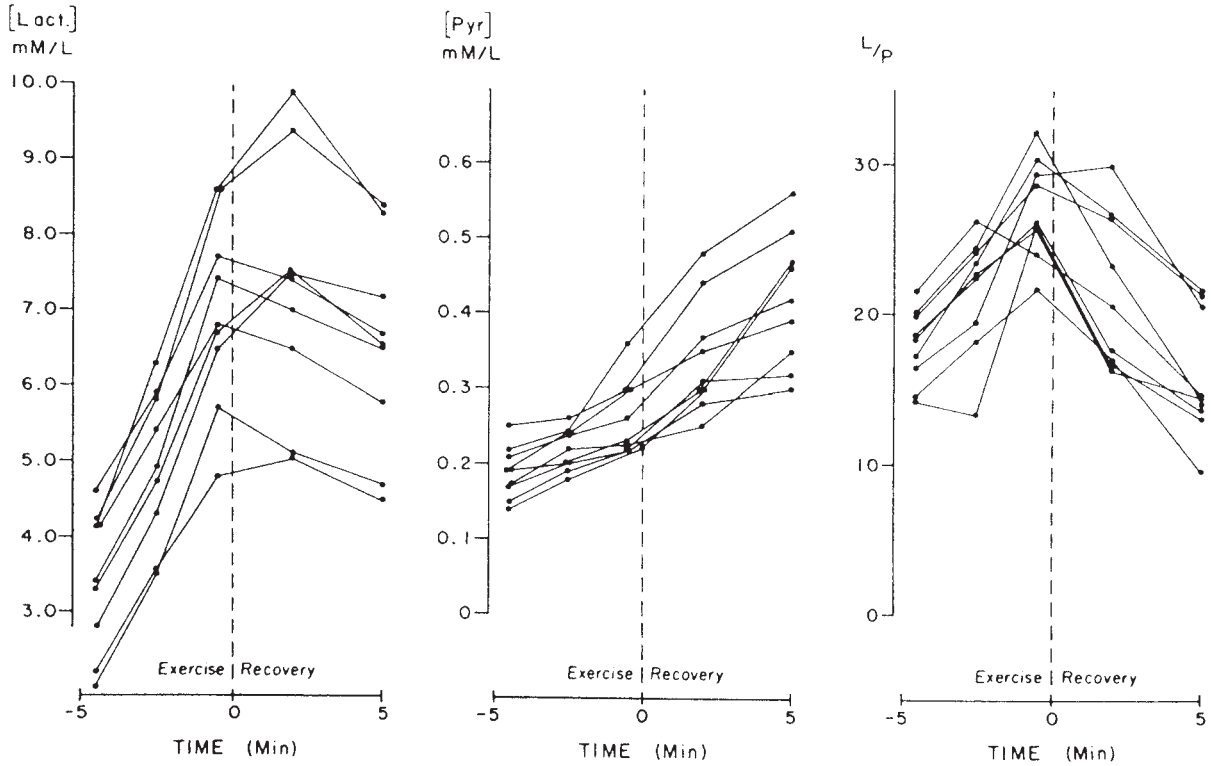

FIGURE 2.14. Lactate (*Lact*), pyruvate (*Pyr*), and lactate-to-pyruvate (L/P) ratio during last 5 minutes (highest three work rates) of exercise and first 5 minutes of recovery. Studies show that lactate either increases or decreases slightly by 2 minutes of recovery. All subjects show a decrease by 5 minutes of recovery. In contrast, pyruvate continues to rise through the first 5 minutes of recovery. As a consequence, L/P ratio decreases by 2 minutes and continues to decrease by 5 minutes of recovery toward control value. (From Wasserman K, Beaver WL, Davis JA, et al. Lactate, pyruvate, and lactate-to-pyruvate ratio during exercise and recovery. *J Appl Physiol.* 1985;59:935–940, with permission.)

cytosolic redox state induced by a net increase in anaerobic glycolysis.

Oxygen Supply, Critical Capillary P_{O_2}, and Lactate Increase

O_2 is consumed by the contracting muscles for the aerobic regeneration of ATP (see Fig. 2.1). Therefore, under the partial pressure gradient, O_2 is extracted from the capillary blood by the actively contracting muscles. Although isolated mitochondria can respire and rephosphorylate ADP to ATP at a P_{O_2} of 1 mm Hg or less,[170] the capillary P_{O_2} must be appreciably greater than 1 mm Hg to provide the O_2 pressure to diffuse from the red cell to the sarcoplasm to sustain muscle mitochondrial respiration during exercise. Wittenberg and Wittenberg estimated this pressure to be 15 to 20 mm Hg.[170] It was termed the *critical capillary* P_{O_2} because it represents the lowest capillary P_{O_2} that allows the muscle mitochondria to receive the O_2 required to perform exercise aerobically. The major factors determining the P_{O_2} difference between red cell and sarcoplasm are the resistances to O_2 diffusion by the red cell membrane, plasma, capillary endothelium, interstitial space, and sarcolemma.[47] By measuring oxymyoglobin saturation in the dog gracilis muscle during a moderate level of exercise, Gayeski and Honig estimated the P_{O_2} in the sarcoplasm to be about 5 mm Hg.[47] The P_{50} for oxymyoglobin in humans is 3 to 6 mm Hg.[46] Because it would be less than one-half saturated, oxymyoglobin can serve as an O_2 store to support only very short bursts of heavy exercise. However, it may play a role in facilitating O_2 diffusion in muscle fibers containing myoglobin.

To obtain a P_{O_2} of 15 mm Hg at the end capillary, a muscle blood flow of at least 6 L would be needed for a muscle O_2 consumption of 1 L/min, assuming a hemoglobin concentration of 15 g/dL and an alveolar P_{O_2} adequate to saturate the arterial oxyhemoglobin to at least 95%. Thus, approximately one-sixth of the O_2 inflow into the capillary bed would remain at the venous end of the capillary.

Figure 2.15 illustrates the change in P_{O_2} along a muscle capillary for various blood flow–metabolic rate ratios ($\dot{Q}m/\dot{V}O_2m$) thought to be physiologic. This model allows for the Bohr effect resulting from aerobic metabolism (decreasing pH in the capillary from aerobic CO_2 production) but not for anaerobic metabolism (lactic acidosis). A blood flow–O_2 consumption ratio of 5:1 would cause obligatory anaerobiosis and lactic acidosis because the muscle capillary P_{O_2} would fall below the critical level

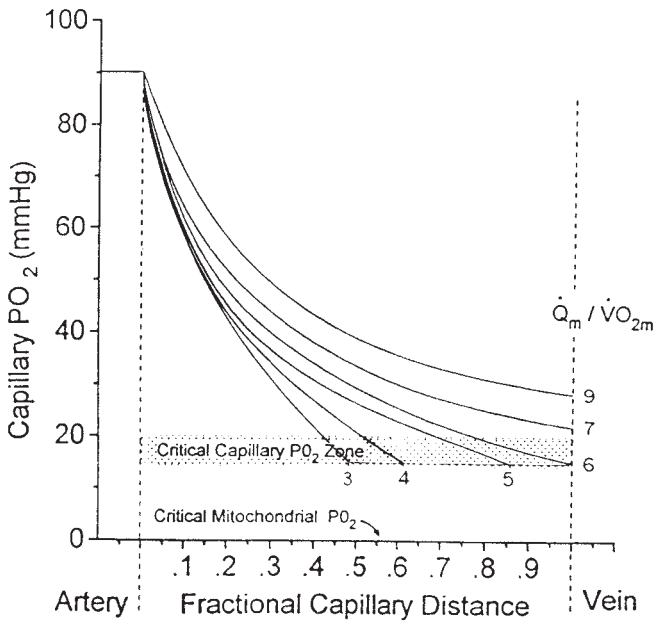

FIGURE 2.15. Model of muscle capillary bed O_2 partial pressure (P_{O_2}) as blood travels from artery to vein. The model assumes hemoglobin concentration of 15 g/dL, arterial P_{O_2} of 90 mm Hg, and a linear O_2 consumption along the capillary. The rate of fall of capillary P_{O_2} depends on the muscle blood flow ($\dot{Q}m$)/muscle $\dot{V}o_2$ ($\dot{V}o_2m$) ratio. The curves include a Bohr effect due to a respiratory Co_2 production. The capillary P_{O_2} is heterogeneous along the capillary bed even with a homogenous $\dot{Q}m$/muscle $\dot{V}o_2$. The end capillary P_{O_2} cannot decrease below the critical capillary P_{O_2}. Any muscle unit with a theoretical $\dot{Q}m/\dot{V}o_2m$ less than 6 will have increased anaerobic metabolism and lactate production. See text for application of model. (From Wasserman K. Coupling of external to cellular respiration during exercise: the wisdom of the body revisited. *Am J Physiol.* 1994;266:E519–E539, with permission.)

before the blood reached the functional venous end of the capillary bed.

Lactic acidosis secondary to cellular hypoxia would be expected only if the critical capillary P_{O_2} was reached in the muscle capillary blood before reaching the vein. When reaching the critical capillary P_{O_2}, capillary blood P_{O_2} could no longer decrease despite increasing work and metabolic rate. As work rate increased further, the critical capillary P_{O_2} would be reached earlier in the course of blood flow through the muscle capillary bed. Thus, lactate would increase in the muscle perfused by capillary blood in which the critical capillary P_{O_2} had been reached—that is, blood toward the venous end of the capillary.

In contrast to the metabolic rate increase of the exercising muscles (including respiratory muscles and heart), the metabolic rates of other tissues do not change appreciably as work rate increases. It may therefore be assumed that the increase in $\dot{V}O_2$ during leg cycling exercise is due primarily to the increase in lower extremity muscle metabolism. Consequently, because the vast majority of the blood flowing past the femoral vein sampling site is from the muscle contracting units, it may be assumed that femoral vein P_{O_2} and lactate closely approximate the average end-capillary values of contracting muscle.

Because the blood enters the muscle with a P_{O_2} of 90 mm Hg (in a normal subject at sea level) and leaves the capillary bed at a P_{O_2} that is approximately equal to that of the femoral vein P_{O_2}, the P_{O_2} in the muscle fiber depends on the anatomical relation between the arterial and the venous end of the muscle capillary bed, and the $\dot{Q}m/\dot{V}O_2m$ ratio of the muscle unit (see Fig. 2.15). The critical capillary P_{O_2} would be the lowest P_{O_2} to which the end-capillary P_{O_2} could fall. The capillary P_{O_2} cannot decrease below the critical capillary P_{O_2} because the mitochondrial P_{O_2} would be too low to consume O_2. That the critical capillary P_{O_2} was reached would be evidenced by the failure of end-capillary or femoral vein P_{O_2} to decrease further despite increasing work rate.

The model shown in Figure 2.15 is instructive in several respects. First, it illustrates that the capillary P_{O_2} is heterogeneous, ranging from high values at the arterial end to low values at the venous end of the capillary bed, even when the muscle $\dot{Q}m/\dot{V}O_2m$ ratios for individual capillary beds in the muscle are homogeneous. It also shows that estimates of mean muscle P_{O_2}, calculated from femoral vein P_{O_2}, are erroneous unless it is certain that there is no heterogeneity in $\dot{Q}m/\dot{V}O_2m$ ratios and that the $\dot{Q}m/\dot{V}O_2m$ ratio is at least 6 (i.e., lactate is not increased). Rather than the mean capillary P_{O_2}, the question must be asked whether the muscle blood flow and therefore capillary P_{O_2} are sufficiently high to prevent a muscle lactic acidosis. When exercise is performed above the *LT*, both aerobic and anaerobic metabolism take place. O_2 is consumed from the blood by the muscle at the arterial end, while lactate is released by muscle on the venous end. If the increase in ATP required exceeds the capability of the circulation to supply O_2 at the rate needed to regenerate the ATP aerobically, the critical capillary P_{O_2} will be reached at the venous end of the muscle capillary.

Experimental support for the critical capillary P_{O_2} concept was provided by the studies of Stringer et al.[126] and Koike et al.[77] in which femoral vein P_{O_2} and lactate were measured during leg cycling exercise in normal subjects and patients with chronic heart failure, respectively. During progressively increasing work rate studies, femoral vein blood P_{O_2} reached a "floor" or lowest value in the middle of the subjects' work capacities and before lactate concentration started to increase (Fig. 2.16). To determine the critical capillary P_{O_2} in normal subjects, 10 healthy adults were studied with femoral vein and arterial catheters, 5 during progressively increasing work rate cycling exercise, and 5 during two levels of constant work rate leg cycling exercise, 1 below and 1 above the *LT*. As would be predicted from the critical capillary P_{O_2} concept, femoral vein and therefore end-capillary P_{O_2} decreased to its lowest value before lactate started to increase (Fig. 2.17). This was true of all subjects, whether performing incremental or heavy constant

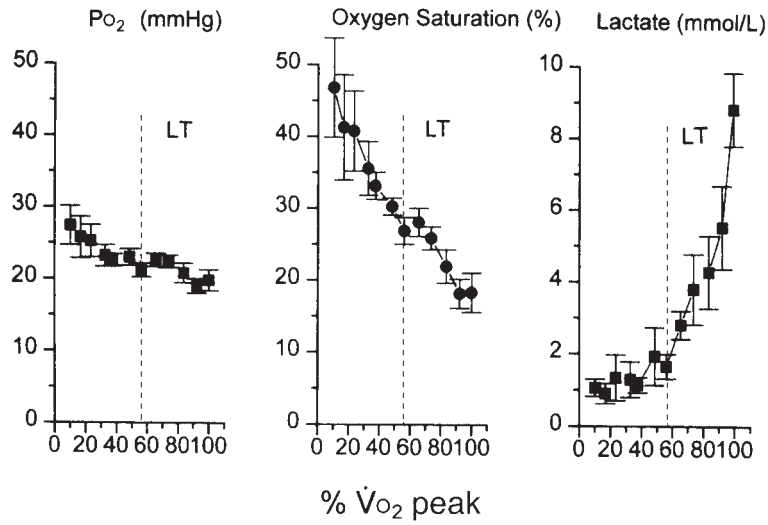

FIGURE 2.16. For five normal subjects, the average femoral vein oxygen tension (P_{O_2}) **(left panel)**, oxyhemoglobin saturation **(middle panel)**, and lactate concentration **(right panel)** during increasing work rate exercise in ramp pattern to the maximal $\dot{V}_{O_2}$. *Vertical dashed line* indicates the average lactate threshold (*LT*) determined by gas exchange using the V-slope method.[12] *Vertical bars* indicate standard error of mean. There is no significant difference between the P_{O_2} values from the *LT* to $\dot{V}_{O_2}$max, but the oxyhemoglobin saturation decreased significantly above the *LT*. (Modified from data reported in Stringer WW, Wasserman K, Casaburi R, et al. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J Appl Physiol.* 1994;76:1462–1467.)

work rate exercise, consistent with the model shown in Figure 2.15. When end-capillary blood reached a floor or critical value of 15 to 20 mm Hg, anaerobic metabolism developed and lactate concentration increased. It is important to note that femoral vein lactate increased before arterial lactate increased, and lactate remained higher in the femoral venous than the arterial blood (Fig. 2.18). This is in agreement with prior studies on lactate balance across the exercising extremity.[5,40,77,125]

To further investigate the hypothesis that femoral vein P_{O_2} reached a floor value by the time the *LT* was reached, normal subjects performed two constant work rate exercise tests for 6 minutes, one at a moderate work rate and one at a heavy work rate. The moderate work rate used was calculated to be at 80% of the *LT* (average = 113 W, $\dot{V}_{O_2}$ = 1.76 L/min). The heavy work rate studied was calculated to be at the *LT* plus 75% of the difference between the *LT* and $\dot{V}_{O_2}$max (average = 265 W, $\dot{V}_{O_2}$ = 3.36 L/min). These tests were done with a high sampling density of femoral vein blood (every 5 seconds during the first 2 minutes and then every 30 seconds for 4 minutes) to accurately describe rapid changes. The results of these studies are shown in Figure 2.19. The femoral vein P_{O_2} decreased to the same floor value at 30 to 60 seconds after the start of exercise for both the moderate and heavy work intensities (see Fig. 2.19, left panel). The femoral vein P_{O_2} values remained unchanged thereafter as the exercise continued in time, and were not different despite the large difference in work rate and $\dot{V}_{O_2}$.

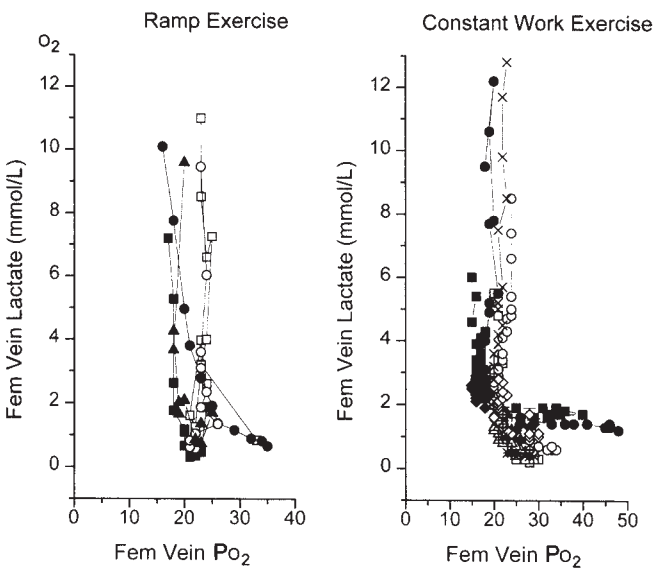

FIGURE 2.17. Femoral vein lactate as function of femoral vein P_{O_2} for incremental (ramp) exercise in five normal subjects **(left panel)** and 10 constant work rate exercise tests (five below and five above the *LT*) in five normal subjects **(right panel)**. The highest P_{O_2} values are where exercise starts. Different symbols represent different subjects. (Modified from Stringer WW, Wasserman K, Casaburi R, et al. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J Appl Physiol.* 1994;76:1462–1467.)

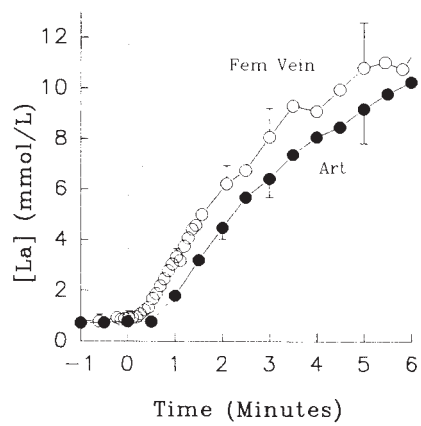

FIGURE 2.18. Average (five normal adult subjects) femoral vein and arterial lactate concentrations during heavy constant work rate leg cycling exercise. By rapid blood sampling, it is clear that the increase in femoral vein lactate precedes the increase in arterial lactate concentration. *Vertical bars* on points are standard errors of the mean.

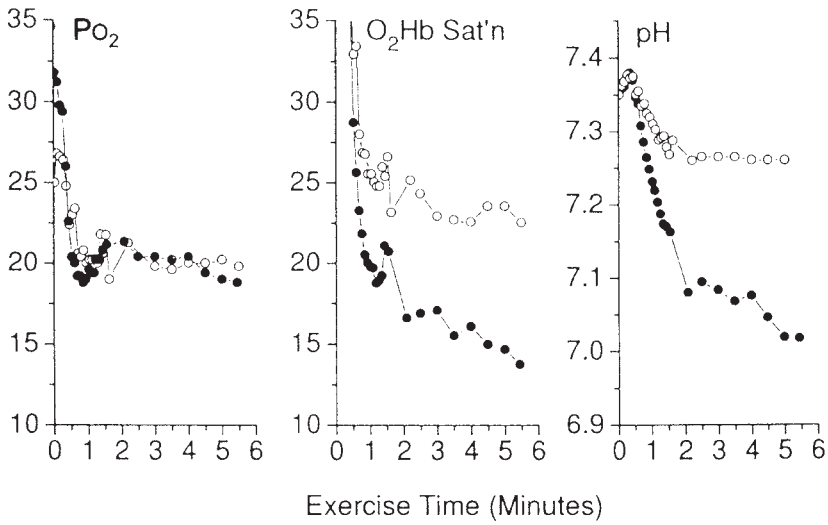

FIGURE 2.19. Femoral venous P_{O_2}, oxyhemoglobin saturation (*O_2Hb Sat'n*) and pH as related to time of exercise for two constant work rate tests, one below (*open circles*) and one above (*solid circles*) the lactate threshold (*LT*). The data are the average of five subjects. The below- and above-*LT* work rates averaged 113 and 265 W, respectively. Note that O_2Hb saturation is lower during the higher-intensity exercise despite identical P_{O_2} values. This is related to the Bohr effect resulting from the decreasing pH in the high-intensity test. (Modified from Stringer WW, Wasserman K, Casaburi R, et al. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J Appl Physiol.* 1994;76:1462–1467.)

In contrast to P_{O_2}, oxyhemoglobin saturation continued to decrease past the time when the end-capillary P_{O_2} (as evidenced from the femoral vein measurements) became constant (see middle panel of Fig. 2.19).

pH Change and Oxyhemoglobin Dissociation above the Lactic Acidosis Threshold

As shown in Figure 2.19, for the work rates selected to be below the *LT*, oxyhemoglobin desaturation proceeded rapidly for the first minute and then more slowly for the next 1 to 2 minutes before reaching a constant value. The change after 1 minute followed the decrease in pH. For the work rate above the *LT*, the oxyhemoglobin desaturation was much more marked and continued for the entire 6 minutes of exercise. The femoral vein oxyhemoglobin desaturation, which was not accounted for by the P_{O_2} decrease, could be completely accounted for by the pH decrease (see Fig. 2.19, right panel). To illustrate this, the data shown in Figure 2.19 were replotted, with femoral vein oxyhemoglobin saturation values plotted against the independently measured femoral vein P_{O_2} values (Fig. 2.20);

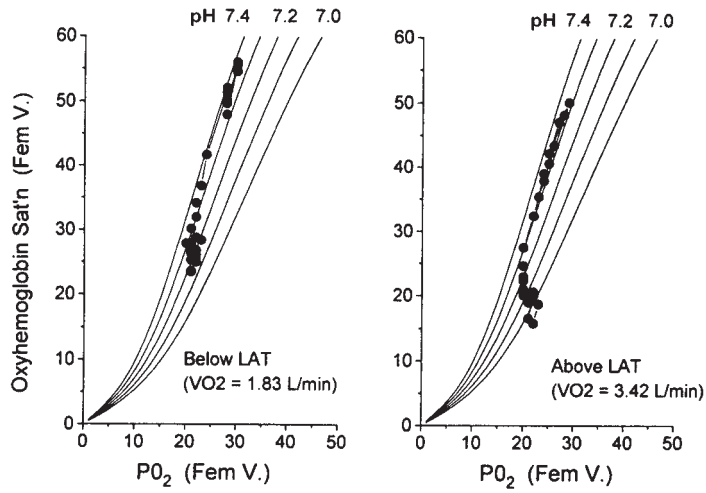

FIGURE 2.20. Changing femoral vein oxyhemoglobin saturation (*O_2Hb Sat'n;* see Fig. 2.19, **middle panel**) as a function of femoral vein P_{O_2} (see Fig. 2.19, **left panel**) for the 6-minute constant work rate exercise tests shown in Figure 2.19. Superimposed are the venous sides of the pH isopleths for oxyhemoglobin dissociation ranging from 7.0 to 7.4, calculated from equations reported by Severinghaus. (Severinghaus JW. Simple accurate equations for human blood O_2 dissociation computations. *J Appl Physiol.* 1979;46:599–602.) **(Left panel)** Data for below lactic acidosis threshold (*LAT*). **(Right panel)** Data for above-*LAT* exercise. Start of exercise is where O_2Hb saturation is highest. Femoral vein oxyhemoglobin saturation progressively decreased as exercise continued, as shown in Figure 2.19. Oxyhemoglobin saturations fell on pH isopleths in agreement with measured pH (see Fig. 2.19, **right panel**). Thus, the entire decrease in O_2Hb saturation that took place after P_{O_2} reached its lowest value could be accounted for by Bohr effect. (From Stringer WW, Wasserman K, Casaburi R, et al. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J Appl Physiol.* 1994;76:1462–1467, with permission.)

pH isopleths are overlaid on these data. It is apparent from this plot that the decrease in oxyhemoglobin saturation below 25% could be accounted for by the decrease in arterial pH (Bohr effect, acidification of the capillary blood) and not a decrease in P_{O_2}.

It is appropriate to distinguish between two terms, the *LT* and lactic acidosis thresholds (*LAT*). As shown in Figure 2.21, HCO_3^- increases when PCr splits, most markedly when the femoral vein P_{O_2} has reached its lowest value. Thus, the first lactate accumulating *LT* is buffered by the new HCO_3^- produced by PCr splitting. After lactate increases by an arterial concentration of 0.5 to 1.0 mmol/L, the arterial blood becomes acidified and HCO_3^- and pH decrease relative to the pre-exercise acid–base status (> *LAT*). The details of the reaction resulting in the formation of HCO_3^- from PCr splitting will be discussed later in this chapter.

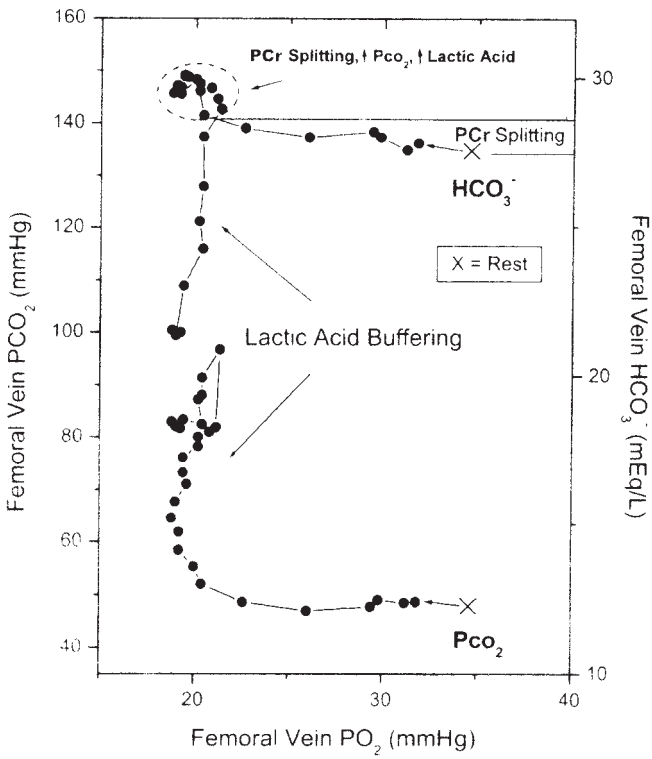

FIGURE 2.21. Change in femoral vein P_{CO_2} and HCO_3^- as P_{O_2} decreases after the start of heavy (85% of $\dot{V}_{O_2}$max) exercise. The direction of change is from the resting value (*X*), leftward. Each subsequent point leftward is recorded from femoral vein blood sampled at 5-second intervals. The increase in femoral vein HCO_3^- during the first 30 seconds occurs without an increase in P_{CO_2}. Thus, this is a true metabolic alkalosis, likely resulting from the splitting of phosphocreatine (PCr) (see text). Lactic acid production starts after the minimal (critical) capillary P_{O_2} is reached (about 18 mm Hg in this figure). Femoral vein HCO_3^- decreases and P_{CO_2} increases due to the HCO_3^- buffering of lactic acid in the exercising muscle, without a further fall in femoral vein P_{O_2}. (The data are the average of five normal subjects, taken from Stringer W, Wasserman K, Casaburi R, et al. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J Appl Physiol.* 1994;76:1462–1467.)

Because the net increase in lactic acid production during exercise is buffered by intracellular HCO_3^-, additional CO_2 is produced in the muscle over that expected from aerobic metabolism as HCO_3^- dissociates. This results in an increase in end-capillary P_{CO_2} without a further fall in P_{O_2} (see lower curve, Fig. 2.21). Simultaneously, the decrease in intracellular HCO_3^- results in a decrease in extracellular HCO_3^-, and therefore femoral vein HCO_3^- (see upper curve, Fig. 2.21). Both the decrease in femoral vein HCO_3^- and the simultaneous increase in P_{CO_2} reflect acidification of the capillary blood of the muscle cells producing lactate.[13,125]

In summary, the lactic acidosis of exercise facilitates oxyhemoglobin dissociation. Consequently, it is an essential mechanism for achieving maximal O_2 extraction while simultaneously maintaining the partial pressure gradient needed to allow O_2 to diffuse into the myocyte at an adequate rate to perform heavy exercise. Thus, for work rates demanding more O_2 than that at the *LAT*, the further extraction of O_2 from oxyhemoglobin is H^+ concentration dependent.

BUFFERING THE EXERCISE-INDUCED LACTIC ACIDOSIS

Lactic acid (as lactate ions and associated protons) is the predominant fixed acid produced during exercise. It has a pK of approximately 3.9 and therefore is essentially totally disassociated at the pH of the muscle cell (approximately 7.0). The H^+ produced in the cell as lactate accumulates must be buffered immediately on its formation. Because HCO_3^- is a volatile buffer, the resulting H_2CO_3 does not remain in the cell but leaves on its formation as CO_2, thereby removing H^+ from the intracellular environment, in contrast to nonvolatile buffers if they were operative. Thus, the nonvolatile buffers would be essentially inoperative for the buffering of the lactic acidosis because the intracellular pH changes minimally due to the volatile HCO_3^- buffer.

Nonaerobic CO_2 production by the cell increases at a rate commensurate with the rate of HCO_3^- buffering of lactic acid. Approximately 22.3 mL CO_2 will be produced over that generated from aerobic metabolism for each mmol of lactic acid buffered by HCO_3^- (see Fig. 2.2). The increase in cell lactate and decrease in cell HCO_3^- concentrations stimulate transmembrane exchange of these ions, with $[HCO_3^-]$ decreasing in the blood almost mmol for mmol with the increase in lactate concentration (Fig. 2.22).[13,16,99,125,131,148,172]

The mechanism for lactate movement out of the cell is primarily carrier mediated. The studies of Trosper and Philipson, working with cardiac sarcolemmal vesicles, suggest that transport is accelerated by the H^+ gradient across the sarcolemmal membrane.[131] At the cellular level, this will be established primarily by the $[HCO_3^-]$ gradient. Mainwood et al.[90] and Hirsche et al.[57] found that lactate efflux from muscle was highly influenced

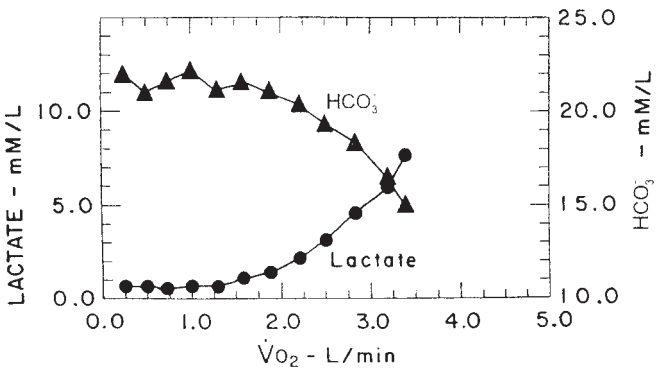

FIGURE 2.22. The increase in arterial lactate and decrease in standard HCO_3^- as related to the increase in O_2 uptake $\dot{V}O_2$ during a progressively increasing work rate test on a cycle ergometer in a normal subject. (Modified from Wasserman K, Beaver WL, Davis JA, et al. Lactate, pyruvate, and lactate-to-pyruvate ratio during exercise and recovery. *J Appl Physiol.* 1985;59:935–940.)

by the HCO_3^- concentration of the muscle perfusate. The reciprocal changes of lactate and HCO_3^- in the extracellular fluid during heavy exercise suggest that permeation of lactate across the sarcolemmal membrane is a coupled HCO_3^-–lactate antiport carrier mechanism. This is supported by the study of Korotzer et al.,[79] which showed that intravenous injection of the carbonic anhydrase inhibitor acetazolamide, prior to performing heavy exercise, significantly attenuates the increase in arterial lactate and decrease in bicarbonate. Replacing the intracellular HCO_3^-, which is consumed when it buffers newly produced lactic acid, with HCO_3^- from the bloodstream minimizes the decrease in intracellular pH.

To better appreciate the dynamics of lactate and HCO_3^- movement between the cell and perfusing blood, arterial lactate and standard (Std) HCO_3^- were measured every 7.5 seconds during the first 3 minutes and then every 30 seconds during the remaining 3 minutes of a 6-minute constant-load exercise at three different intensities: moderate, heavy, and very heavy (Fig. 2.23). For the latter two work intensities, lactate started to increase at about 40 seconds and Std HCO_3^- started to decrease at about 50 seconds. Thereafter, lactate and Std HCO_3^- changed reciprocally. Figure 2.24 shows the simultaneous decrease in Std HCO_3^- and lactate increase for all arterial samples for heavy and very heavy exercise intensities for the eight subjects whose data contributed to the concentration-time plots shown in Figure 2.23. The arterial Std HCO_3^- decrease and lactate increase were highly correlated, mmol for mmol,

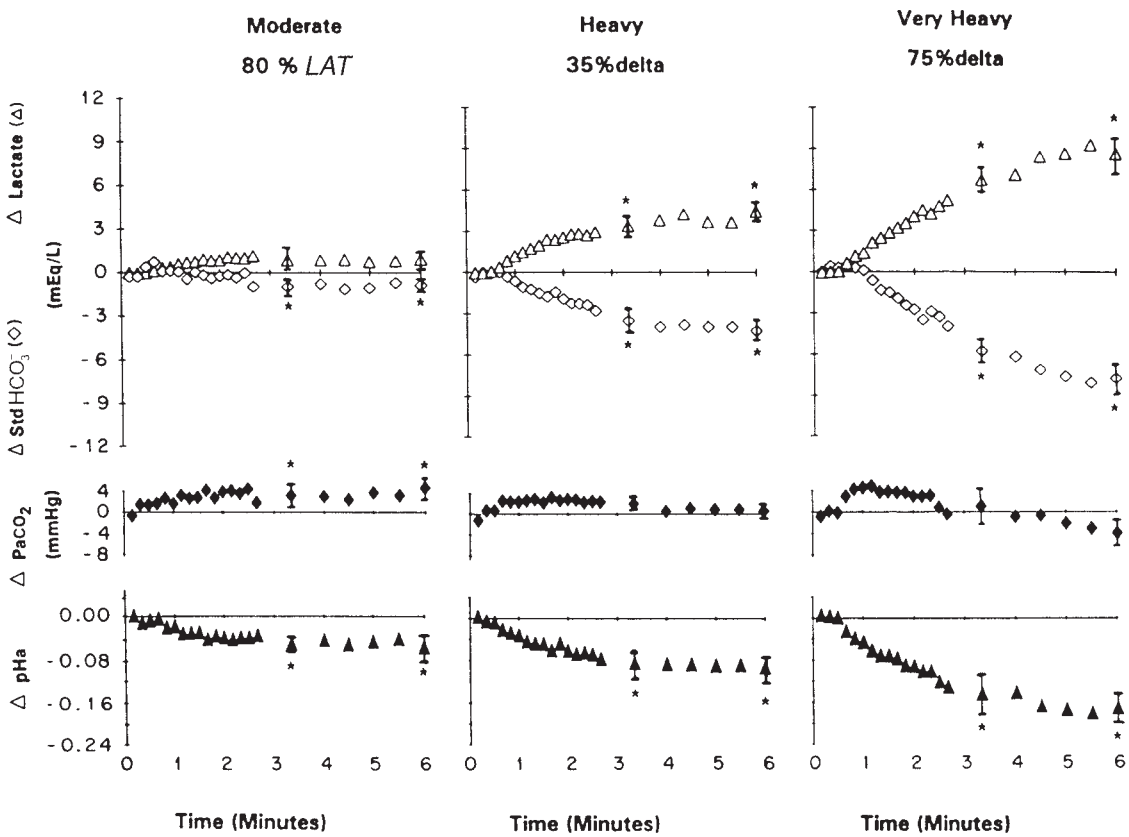

FIGURE 2.23. Average responses to three exercise intensities displayed as change from resting measurements for arterial lactate, standard bicarbonate (Std HCO_3^-), P_{CO_2}, and pH (n = 8 subjects). Resting values for arterial pH, P_{CO_2}, standard HCO_3^-, lactate, and hemoglobin are 7.40 ± 0.03 (standard deviation), 39.8 ± 3.1 torr, 24.5 ± 1.3 mEq/L, 0.89 ± 0.47 mEq/L, and 14.2 g/dL, respectively. Significant differences from baseline (zero time) are shown at 3 and 6 minutes (*$P < .05$ from rest). (From Stringer W, Casaburi R, Wasserman K. Acid-base regulation during exercise and recovery in man. *J App Physiol.* 1992;72:954–961, with permission.)

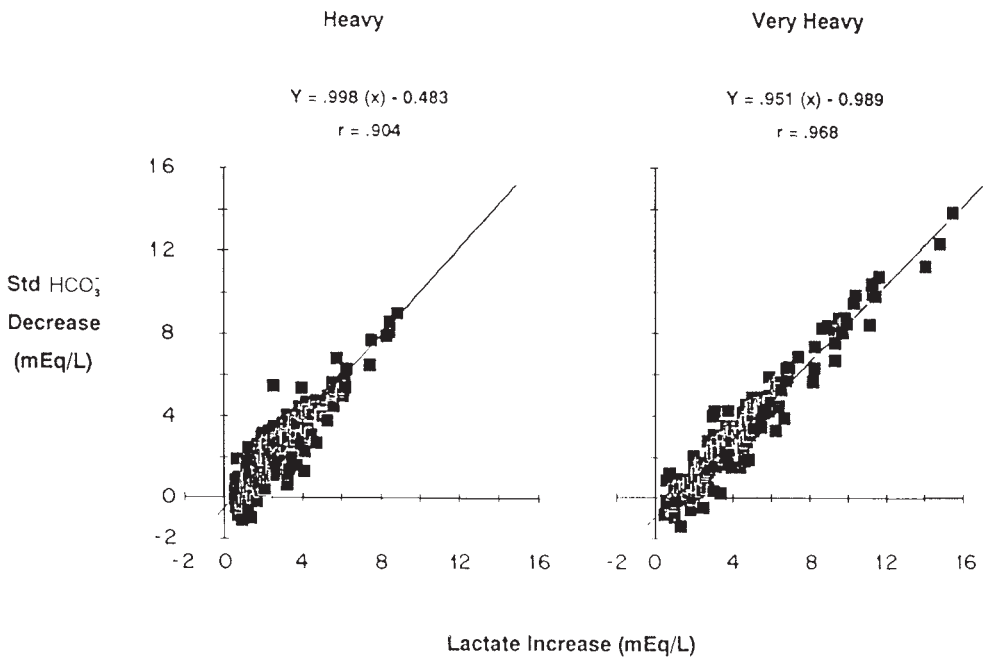

FIGURE 2.24. Standard (Std) HCO_3^- decrease as a function of lactate increase from resting values for the heavy and very heavy work intensities shown in Figure 2.23. Fall in Std HCO_3^- is delayed until after lactate starts to increase (see regression equations). Thereafter, changes are approximately equal and opposite [heavy n = 181: slope = 0.998 (CI 0.92 to 1.06), intercept = – 0.48 (CI – 0.71 to – 0.26); very heavy, n = 141: slope = 0.951 (CI 0.92 to 0.98), intercept = – 0.99 (CI – 1.12 to – 0.78)]. (From Stringer W, Casaburi R, Wasserman K. Acid-base regulation during exercise and recovery in man. *J Appl Physiol.* 1992;72: 954–961, with permission.)

after lactate increased by about 0.5 mmol/L and 1.0 mmol/L for heavy and very heavy intensity exercise, respectively (see Fig. 2.24), The earliest H^+ produced with lactate is buffered by a mechanism entailing the hydrolysis (splitting) of PCr, primarily within the first minute of exercise. This reaction produces new HCO_3^- buffer.

This development of a metabolic alkalosis during the first 30 to 60 seconds of exercise accounts for the failure of arterial HCO_3^- to decrease until lactate increased by approximately 0.5 to 1.0 mmol/L. The release of muscle K^+, as well as the development of muscle and femoral vein metabolic alkalosis, is thought to be due to the increase in intracellular pH caused by the hydrolysis of PCr (Fig 2.25 and 2.26).[147] This early exercise-induced metabolic alkalosis masks the initial metabolic acidosis caused by the increase in lactate. Thus, the *LT* (i.e., the $\dot{V}O_2$ above which there is a sustained lactate increase) slightly precedes the decrease in arterial Std HCO_3^-. Consequently, the *LAT* develops at a slightly higher $\dot{V}O_2$ as compared to that of the *LT*, as previously shown by Beaver et al.[13] and Stringer et al.[125]

The *LAT* contrasts with the *LT* in methodology only. The latter is determined from actual measurements of arterial lactate increase, whereas the former is determined by the decrease in arterial HCO_3^- concentration due to its buffering of newly accumulating lactic acid. It can also be defined by the gas exchange consequence of the HCO_3^- buffering of the lactic acid—that is, the CO_2 derived from

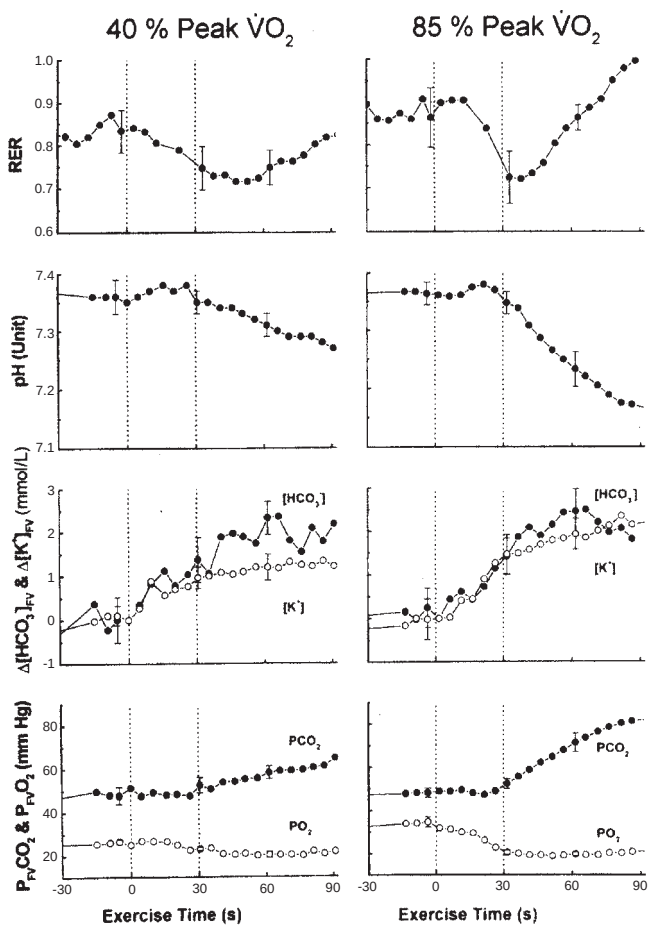

FIGURE 2.25. Respiratory exchange ratio (RER, **upper panels**), femoral vein pH **(panels second from top)**, change (Δ) in femoral vein HCO_3^- and K^+ concentration **(panels third from the top),** and femoral vein P_{CO_2} and P_{O_2} **(bottom panels)** in response to the start of exercise (zero time) for the first 90 seconds of upright leg cycling exercise at 40% **(left panels)** and 85% **(right panels)** of $\dot{V}O_{2peak}$. Each point is the average of five subjects. *Vertical bars* on select points are standard error values. (Modified from Wasserman K, Stringer W, Casaburi R, et al. Mechanism of the exercise hyperkalemia: an alternate hypothesis. *J Appl Physiol.* 1997;83:631–643.)

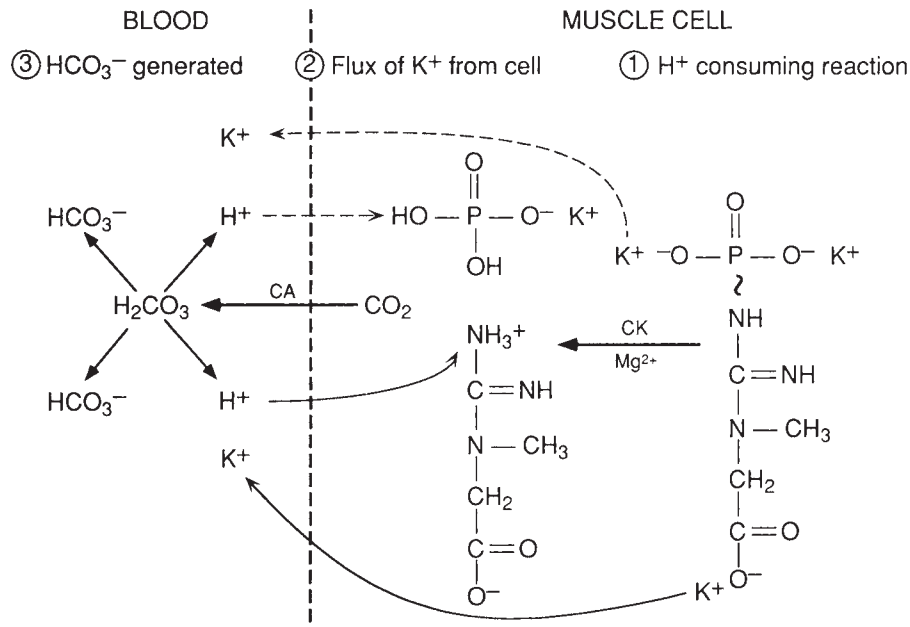

FIGURE 2.26. Hypothesis describing the mechanism for early changes in femoral vein pH, HCO_3^-, and K^+ in response to exercise. *Step 1* shows that when phosphocreatine (PCr) is hydrolyzed into creatine and inorganic phosphate, H^+ is consumed, resulting in a reduction of negative charges in the cell and an alkalinizing reaction. *Step 2* illustrates that the excess in intracellular cation and a shortage of H^+ causes K^+ to leave the cell and H^+ to enter the cell. *Step 3* shows that the resulting efflux of K^+ from the cell is balanced by newly formed HCO_3^- in the interstitial fluid and therefore the effluent blood of the muscle. Thus, metabolic CO_2, when hydrated, becomes H_2CO_2, which dissociates into H^+ (which is taken up by the alkaline myocyte) and HCO_3^- anion (which serves to balance the positive charge of K^+). (From Wasserman K, Stringer W, Casaburi R, et al. Mechanism of the exercise hyperkalemia: an alternate hypothesis. *J Appl Physiol.* 1997;83:631–643, with permission.)

the dissociation of HCO_3^- as it buffers lactic acid. The *LT* and *LAT* are systematically related and conceptually interchangeable, but there is a small quantitative difference between them.

THE ANAEROBIC THRESHOLD CONCEPT

The finding that the lactic acidosis of exercise does not take place until a minimum P_{O_2} is reached in the muscle venous effluent supports the concept that lactate accumulation starts when the muscle O_2 supply becomes critical. Thus, the anaerobic threshold (*AT*), measured by arterial lactate increase, arterial HCO_3^- decrease, or the CO_2 generated from the HCO_3^- buffering of lactic acid,[141] describes the $\dot{V}O_2$ at which the critical capillary P_{O_2} has been reached for a given work task.

That the lactic acidosis of exercise results from muscle hypoxia is further supported by the observation that the muscle L/P ratio, a measure of the cell redox state, increases when the *LT* is reached.[22,69,117] Arterial blood lactate and pyruvate measurements in humans show that the arterial L/P ratio increases at the *LT*.[143] Because the cytosolic $[NADH + H^+]/NAD^+$ ratio is regulated by the mitochondrial redox state through the mitochondrial membrane shuttle (see Fig. 2.1), failure to reoxidize mitochondrial coenzymes with molecular O_2 would also limit the reoxidation of cytosolic $[NADH + H^+]$ to NAD^+.

Experimental observations demonstrate that blood lactate concentration can be reduced or increased as a result of increases or decreases, respectively, in blood oxygenation.[35,76,88,132,171] For example, increasing blood O_2 content during exercise above the *LT* reduces arterial blood lactate. In contrast, reducing arterial blood O_2 content increases blood lactate.[88,140] The diversion of pyruvate from the tricarboxylic acid cycle to the production of cytosolic lactate results in accelerated use of carbohydrate stores.[35,60] Thus, the rate of anaerobic glycolysis is affected by blood oxygenation.

The Anaerobic Threshold and Oxygen Uptake–Independent and –Dependent Work Rate Zones

The *AT* concept implies that there is an exercise $\dot{V}O_2$ below which exercise $\dot{V}O_2$ is determined by the work rate performed and not the O_2 transport to the muscles and above which $\dot{V}O_2$ is determined by O_2 transport as well as the work rate. In other words, below the *AT*, $\dot{V}O_2$ is insensitive to O_2 flow, and above the *AT*, $\dot{V}O_2$ is sensitive to O_2 flow. To test this hypothesis, Hansen et al.[53] increased work rate at slow, medium, and fast rates and found that below the *AT*, $\dot{V}O_2$ increased at a rate that did not vary with the rate of increase in work rate; in contrast, $\dot{V}O_2$ decreased for a given work rate—faster as the work rate increased above the *AT* (Fig. 2.27),—without a change in peak $\dot{V}O_2$.

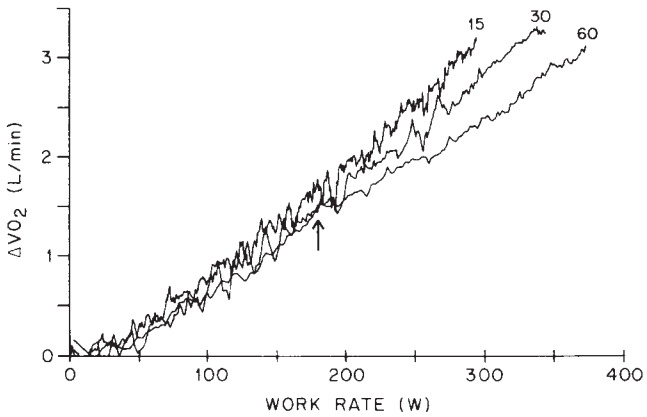

FIGURE 2.27. Effect of rate of increase in work rate from unloaded cycling on rate of increase in $\dot{V}O_2$ in a normal subject. Below the anaerobic threshold (approximately 180 W, *arrow*), the rate of increase in $\dot{V}O_2$ is independent of the rate of increase in work rate. Above the anaerobic threshold, the increase in $\dot{V}O_2$ is slower the faster the rate of increase in work rate, although the peak $\dot{V}O_2$ is unchanged. (From Hansen JE, Sue DY, Oren A, et al. Relation of oxygen uptake in work rate in normal men and men with circulatory disorders. *Am J Cardiol.* 1987;59:669–674, with permission.)

The failure of $\dot{V}O_2$ to fully track work rate change above as compared to below the *AT* was also shown by Haouzi et al.[54] Work rate was changed in equal sine-wave pattern, period and magnitude below and above the *AT* (Fig. 2.28). Below the *AT*, the amplitude in $\dot{V}O_2$ varied with the amplitude of work rate in an approximate ratio of 10 mL/min/W. In contrast, the amplitude of change in $\dot{V}O_2$ for the same period and work rate change was only about two-thirds above the *AT*. This reduction in the $\dot{V}O_2$–work rate relationship supports the hypothesis that $\dot{V}O_2$ does not reach the O_2 requirement above the *AT*.

Koike et al. also demonstrated that the *AT* demarcates the O_2 flow–independent from the O_2 flow–dependent work rate zones.[76,78] In their study, blood O_2 content was decreased in a controlled fashion in normal subjects by taking up O_2 binding sites on hemoglobin with carbon monoxide (Fig. 2.29). The blood O_2 content was reduced by approximately 10% and 20% before performing exercise. The *AT* and peak $\dot{V}O_2$ were reduced by a percentage consistent with the percentage reduction in blood O_2 content. Although $\dot{V}O_2$ increased at an unchanged rate for different levels of carboxyhemoglobin (COHb) at the work rates below the *AT*, the rate of increase in $\dot{V}O_2$ was reduced for the work rates above the *AT* with increases in COHb.

Identifying the Anaerobic Threshold by Gas Exchange

Figure 2.30 shows the effect of an increasing work rate on ventilation and gas exchange for a cycle ergometer exercise test in which the work rate was increased at 1-minute intervals after a 4-minute warmup period of pedaling without load. As the work rate is increased, $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ increase linearly with work rate, after a time delay of less than 1 minute, until the exercise lactic acidosis developed. At work rates above the *LAT*, CO_2 output increased more rapidly than O_2 uptake because CO_2, which is generated by the bicarbonate buffering of lactic acid, is added to the CO_2 produced by aerobic metabolism. This is the basis of the V-slope method for measuring the *AT* (described later in the chapter).[12]

Isocapnic Buffering Period above the Anaerobic Threshold

When performing progressively increasing work rate, $\dot{V}E$ increases linearly with CO_2 output over a wide range of work rates. The typical breath-by-breath gas exchange measurements during progressively increasing work rate are shown with the simultaneous arterial lactate and acid-base changes for a normal subject in Figure 2.30. When the lactic acidosis first develops, both $\dot{V}CO_2$ and

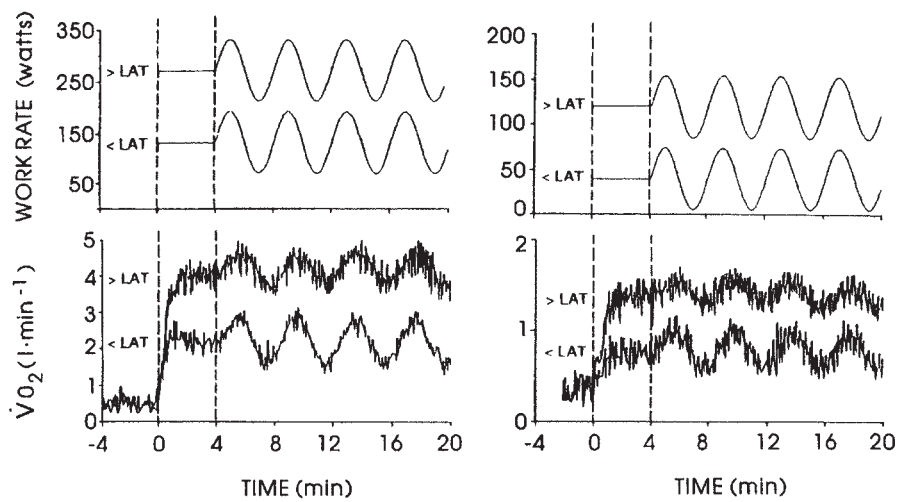

FIGURE 2.28. Effect of continuously changing work rate in sinusoidal pattern (**upper panel**) on $\dot{V}O_2$ kinetics (**lower panel**) for a range of changing work rates below (<*LAT*) and above (>*LAT*) the lactic acidosis (anaerobic) threshold (*LAT*). (From Haouzi P, Fukuba Y, Casaburi R, et al. O_2 uptake kinetics above and below the lactic acidosis threshold during sinusoidal exercise. *J Appl Physiol.* 1993;75:1644–1650, with permission.)

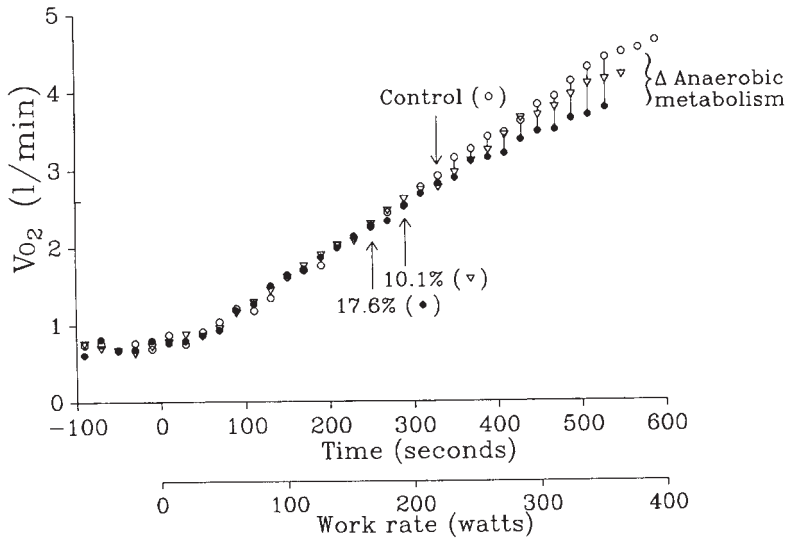

FIGURE 2.29. $\dot{V}O_2$ response to three ramp tests (work rate increased at 40 W/min) during air breathing (control test) and two tests of air plus carbon monoxide breathing that resulted in COHb levels of 10.1% and 17.6%, respectively, in one subject. Points to the left of 0 are measured during unloaded cycling. Each point is an average of 20 seconds of data. The order of tests was randomized. There was no effect on $\dot{V}O_2$ as work rate was increased until the anaerobic threshold (*AT, arrow)* of the respective study was surpassed. Then the increase in $\dot{V}O_2$ was slower the higher the COHb. The difference between the $\dot{V}O_2$ of the control and the reduced blood O_2 content studies represents the reduction in $\dot{V}O_2$ caused by the reduced blood O_2 content. The *AT* and peak $\dot{V}O_2$ systematically decreased as the blood O_2 content was decreased. The difference enclosed by brackets on the right is the metabolic equivalent of increased anaerobic metabolism caused when COHb was increased to 17.6%. (From Koike A, Weiler-Ravell D, McKenzie DK, et al. Evidence that the metabolic acidosis threshold is the anaerobic threshold. *J Appl Physiol.* 1998:2521–2526, with permission.)

$\dot{V}E$ increase curvilinearly, resulting in no further change in $\dot{V}E/\dot{V}CO_2$ and $PETCO_2$ (isocapnic buffering, Fig. 2.30). Thus, $\dot{V}E$ retains a linear relation with $\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$ is constant or decreases slightly) while it increases relative to $\dot{V}O_2$ ($\dot{V}E/\dot{V}O_2$ increases) above the *LAT* (Fig. 2.30). As described in Chapter 4, the increase in $\dot{V}E/\dot{V}O_2$ without an increase in $\dot{V}E/\dot{V}CO_2$ is a gas exchange method for detecting the *AT*.[154]

$\dot{V}E$ increases more rapidly than $\dot{V}CO_2$ (increase in $\dot{V}E/\dot{V}CO_2$) after the isocapnic buffering period. This is the ventilatory compensation point (VCP). The increase in $\dot{V}E$ relative to $\dot{V}CO_2$ is associated with a decrease in $PaCO_2$ and $PETCO_2$ (see Fig. 2.30). The increased H^+ concentration stimulates the carotid bodies to increase ventilatory drive.[152] By increasing the ventilatory drive, arterial PCO_2 is reduced, providing a ventilatory constraint to the lactic acid–induced fall in pH.[155] This additional ventilatory response reflects the ventilatory compensation for the exercise-induced lactic acidosis.

Buffering Lactic Acid and the V-Slope Method for Identifying the Anaerobic Threshold

Figure 2.2 shows the effect of HCO_3^- buffering the cellular lactic acidosis on $\dot{V}CO_2$ relative to $\dot{V}O_2$. The increases in $\dot{V}O_2$ and $\dot{V}CO_2$ as a function of progressively increasing work rate are shown in Figure 2.31. Plotting $\dot{V}CO_2$ as a function of $\dot{V}O_2$ for a progressively increasing work rate test (V-slope plot), after the first minute or so of increasing work rate, yields a progression of points that are commonly linear with a slope of 1.0 or slightly less. The slope then breaks, with $\dot{V}CO_2$ increasing faster than $\dot{V}O_2$ so that the new slope is now clearly above 1.0. The breakpoint where the slopes coincide is the anaerobic or lactic acidosis threshold (Fig. 2.32), as confirmed with arterial standard HCO_3^- measurements. It is *slightly* higher than the *LT* for the reasons described earlier in this section. The slope of the increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$ below the threshold (see S_1 in Fig. 2.32) has an average value of 0.95, with a small variation.[10,34] The transition to a slope greater than 1.0 (see S_2 in Fig. 2.32) occurs, on average, in the mid-range of healthy subjects' aerobic capacities.

The $\dot{V}CO_2$ versus $\dot{V}O_2$ Slopes

The intercept of S_1 and S_2 of the $\dot{V}CO_2$ versus $\dot{V}O_2$ relationship is the *LAT*, measured by gas exchange, and estimates the *AT*. The term *lactic acidosis threshold* describes the biochemical event that causes the $\dot{V}CO_2$ versus $\dot{V}O_2$ slope to exceed 1. Hyperventilation (reduction in $PaCO_2$ and increase in $\dot{V}O_2$) during rapidly incremental work rate profiles almost never occurs at the *LAT* or for several minutes thereafter. When hyperventilation does occur during a progressively increasing work rate test, it does so at a higher $\dot{V}O_2$ (at the upper downward-directed arrow in Fig. 2.32) and represents the ventilatory compensation

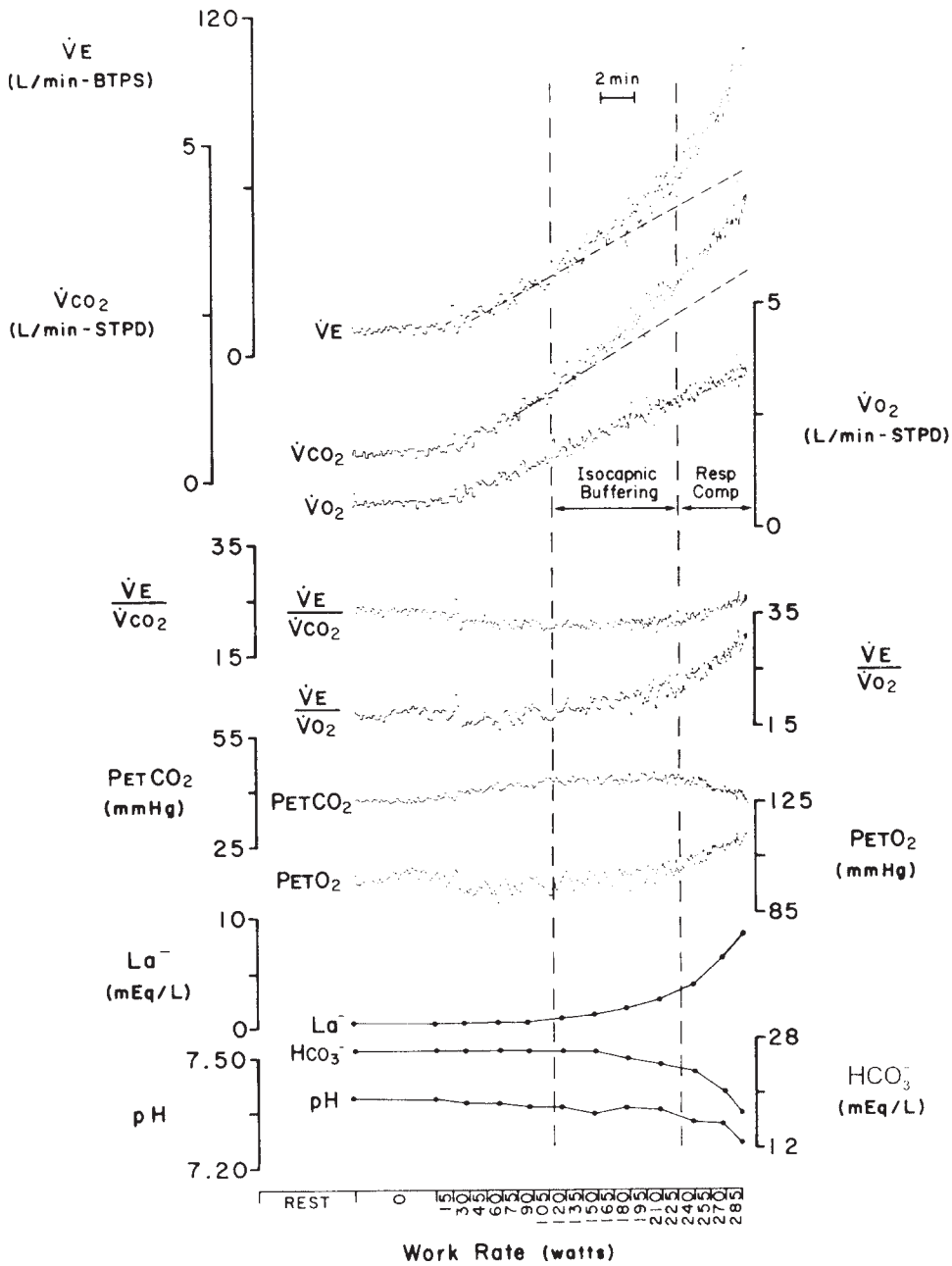

FIGURE 2.30. Breath-by-breath measurements of minute ventilation ($\dot{V}E$), CO_2 output ($\dot{V}CO_2$), O_2 uptake ($\dot{V}O_2$), $\dot{V}E/\dot{V}CO_2$, $\dot{V}E/\dot{V}O_2$, $P_{ET}CO_2$, $P_{ET}O_2$, arterial lactate and bicarbonate, and pH for a 1-minute incremental exercise test on a cycle ergometer. The lactate threshold (*LT*) occurs when lactate increases (*left vertical dashed line*). This is followed by a fall in HCO_3^- *(LAT)* and generally an increase in $\dot{V}E/\dot{V}O_2$. *Isocapnic buffering* refers to the period when $\dot{V}E$ and $\dot{V}CO_2$ increase curvilinearly at the same rate without an increase in $\dot{V}E/\dot{V}CO_2$, thus retaining a constant $P_{ET}CO_2$. After the period of isocapnic buffering, $P_{ET}CO_2$ decreases and $\dot{V}E/\dot{V}CO_2$ increases, reflecting ventilatory compensation for the metabolic acidosis of exercise.

for the lactic acidosis. When S_2 is steeper than a slope of 1.0 during the progressively increasing work rate test, it signifies that CO_2 is being released from HCO_3^- as it dissociates when buffering lactic acid (see Fig. 2.2).

It has been demonstrated that S_2 becomes steeper than S_1 the faster the work rate increases,[34,119,137] presumably because of the faster rate of lactate formation relative to $\dot{V}O_2$ increase. However, with glycogen depletion, S_1 becomes shallower, consistent with the lower respiratory quotient of the muscle metabolic substrate.[34]

Anaerobic, Lactate, and Lactic Acidosis Thresholds

Anaerobic glycolysis supplements the aerobic ATP-regenerating mechanism, resulting in increases in lactate

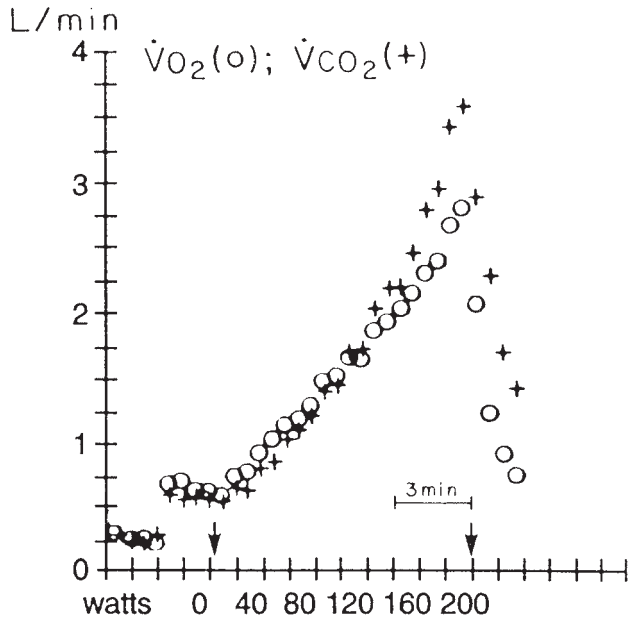

FIGURE 2.31. $\dot{V}CO_2$ and $\dot{V}O_2$ as related to work rate for 1-minute incremental (20 W/min) cycle ergometer exercise test. $\dot{V}CO_2$ starts to increase more steeply than $\dot{V}O_2$ in the middle work rate range, reflecting buffering of lactic acid above the lactic acidosis threshold.

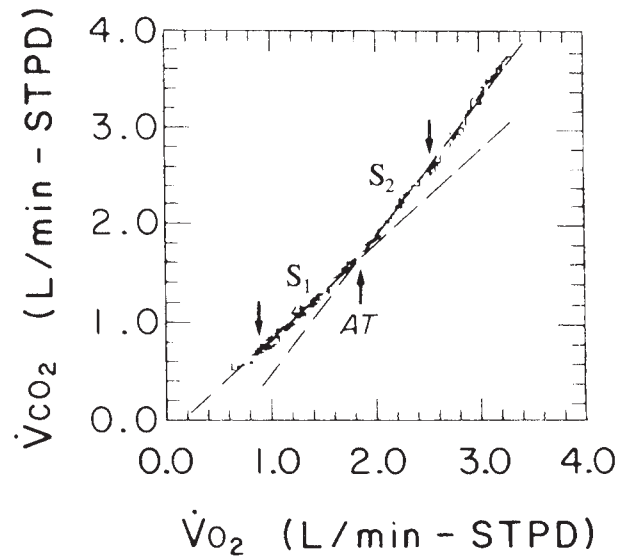

FIGURE 2.32. CO_2 output ($\dot{V}CO_2$) as a function of oxygen uptake ($\dot{V}O_2$) during a progressively increasing work rate test (V-slope plot). The transition from aerobic metabolism, where $\dot{V}CO_2$ increased linearly with $\dot{V}O_2$ with a slope (S_1) slightly less than 1, to anaerobic plus aerobic metabolism, where the slope increased to a value greater than 1 (S_2), defines the lactic acidosis threshold *(LAT)* or anaerobic threshold *(AT)* by gas exchange. The steeper S_2 reflects the production of additional CO_2 from HCO_3^- buffering of lactic acid over that produced by aerobic metabolism. Hyperventilation does not occur at the *AT* during a progressively increasing work rate test and therefore does not contribute to the steepening of S_2. The *lower downward-directed arrow* indicates where CO_2 stores are no longer increasing and calculation of S_1 starts. The *upper downward-directed arrow* indicates the $\dot{V}O_2$ above which hyperventilation in response to metabolic acidosis starts. S_1 and S_2 are calculated from the data between the two down arrows. (Modified from Beaver WL, Wasserman K, Whipp BJ. A new method for detecting the anaerobic threshold by gas exchange. *J Appl Physiol.* 1986;60:2020–2027.)

and L/P ratio, when aerobic regeneration of ATP is partially limited by an inadequate O_2 supply. This $\dot{V}O_2$ has been termed the *anaerobic threshold* (*AT*).[145]

The *AT*, *LT*, and *LAT* are all part of the same physiological phenomenon, an O_2 supply/demand imbalance in the muscle. The distinction in terminology describes the method of measurement and does not dispute their common underlying mechanism, anaerobic metabolism.[100] Although these terms are often used interchangeably, we regard the technically correct definitions to be as follows:

- *Anaerobic threshold:* The exercise $\dot{V}O_2$ above which anaerobically produced high-energy phosphate (~P) supplements the aerobically produced ~P, with consequent lowering of the cytosolic redox state, increasing L/P ratio, and lactate production at the site of cellular anaerobiosis.
- *Lactate threshold:* The exercise $\dot{V}O_2$ above which a net increase in lactate production is observed to result in a sustained increase in lactate concentration in the circulating blood, accompanied by an increase in L/P ratio.
- *Lactic acidosis threshold:* The exercise $\dot{V}O_2$ above which arterial standard HCO_3^- (the principal buffer of lactic acid) is observed to decrease because of a net increase in lactic acid production (Fig. 2.33). During an increasing work rate exercise test, this can be detected by an increase in CO_2 output above that which would be predicted from aerobic metabolism (because of dissociation of HCO_3^- as it buffers lactic acid). The threshold measured by gas exchange is the *AT* or *LAT* (see Fig. 2.33).

Altered Physiological Responses to Exercise above the Anaerobic Threshold

The *AT* appears to be an excellent discriminator of the highest work rate that can be endured for a prolonged period of exercise, such as a marathon.[130,178] $\dot{V}O_2$ and $\dot{V}E$ reach a steady state early for exercise at or below the *AT*. However, a steady state in $\dot{V}O_2$ and $\dot{V}E$ is delayed or not achieved for exercise above the *AT*. Acid–base balance is essentially unchanged from rest for work rates below the *AT* (acid–base homeostasis). In contrast, there is a metabolic acidosis above the *AT*, with $PaCO_2$ decreasing several minutes after lactic acidosis develops.

Table 2.2 lists the physiological changes that take place when performing exercise above the *AT*. These include important functional adaptations that affect ATP production and mitochondrial O_2 supply, such as further vasodilatation in the vascular bed with high H^+ production,[41] a shift in the oxyhemoglobin

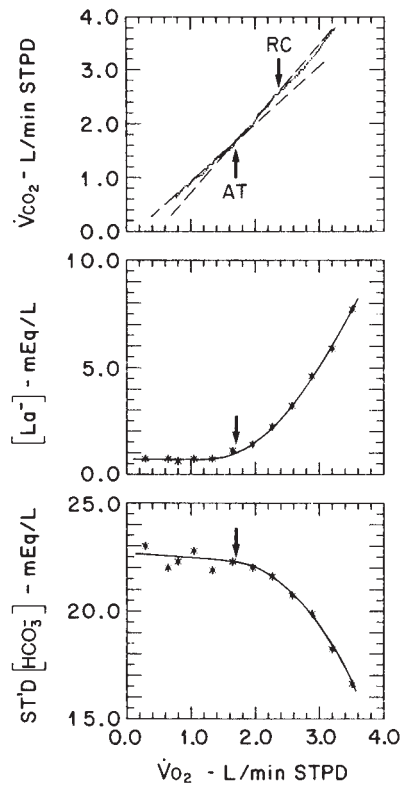

FIGURE 2.33. Plots of arterial lactate and standard HCO_3^- concentrations and $\dot{V}co_2$ as a function of $\dot{V}o_2$ for a single subject. *Arrows* indicate estimates of the anaerobic threshold *(AT)* by the $\dot{V}co_2$ vs. $\dot{V}o_2$ (V-slope) plot, and arterial lactate increase and HCO_3^- decrease versus $\dot{V}o_2$. RC is the respiratory compensation point.

dissociation curve to the right, allowing O_2 to unload more readily from hemoglobin,[74] and increase in hemoglobin concentration.[66] A description of the physiological responses to exercise that are altered above the *AT* follows.

Accelerated Glycolysis

Hill and associates[56] showed a correlation between blood lactate increase and the O_2 debt (the amount of O_2 consumed, over resting levels, during the recovery from exercise). When the mechanism for glycolysis was better understood, it was appreciated that three ATP molecules were generated during the anaerobic metabolism of one glycosyl unit of glycogen with the production of two lactate molecules.[95] By this mechanism, anaerobic glycolysis provides energy without use of molecular oxygen (see Fig. 2.1). Although this mechanism provides ATP without use of O_2, the ATP yield from each glycosyl molecule, anaerobically metabolized to lactate, is only one-twelfth of that from each glycosyl aerobically metabolized to CO_2 and H_2O. Thus, the rate of glycogen utilization in muscle is markedly accelerated above the *AT*, thereby depleting muscle glycogen stores relatively rapidly.

Exercise Endurance

Exercise endurance is reduced for work rates above the *LT* or *AT*, the reduction being greater the higher the blood lactate that the exercise engenders (see Fig. 2.11). Reduced endurance may not be due to the increased lactate concentration or the associated increase in H^+ per se, but rather factors linked to the inadequate rate of ATP regeneration needed to sustain muscle contraction.

Oxyhemoglobin Dissociation

The increase in H^+ in the muscle capillary bed caused by the lactic acidosis of above *LAT* exercise facilitates the dissociation of oxygen from hemoglobin (Bohr effect)—that is, a rightward shift in the oxyhemoglobin dissociation curve. This mechanism maintains the critical capillary P_{O_2} while allowing O_2 to dissociate from

Table 2.2

Altered Physiological Responses to Exercise above the Anaerobic Threshold

1. Accelerated muscle glycogen utilization and anaerobic regeneration of adenosine triphosphate
2. Reduced exercise endurance
3. Metabolic acidosis
4. Delay in $\dot{V}O_2$ steady state
5. Increased $\dot{V}CO_2$ over that predicted from aerobic metabolism
6. Increased ventilatory drive
7. Decreasing $PaCO_2$ and $PETCO_2$ with time
8. Bohr effect rather than decreasing capillary P_{O_2} increases O_2 extraction from blood
9. Increased plasma electrolyte concentration
10. Hemoconcentration
11. Increased production of metabolic intermediaries (e.g., glycerol phosphate and alanine)
12. Increased catecholamine levels
13. Increased double product

hemoglobin to maintain oxidative metabolism for ATP regeneration.[141] Thus, in McArdle's syndrome or other disorders of glycolysis in which lactate cannot increase, it is not possible to extract O_2 to the extent seen in normal subjects during maximal exercise.[84] This has been experimentally demonstrated by the reduced arterial-venous O_2 difference at the exercise work rate at which the patient with McArdle's syndrome is forced to stop exercise due to muscle pain or fatigue.[84] While P_{O_2} remains constant at its critical value above the *AT* in healthy subjects, end-capillary oxyhemoglobin saturation continues to decrease in accordance with the pH decrease. Thus, for normal extraction of O_2 by the muscles, two factors—decreasing P_{O_2} and increasing H^+—are required. The former plays a more important role in oxyhemoglobin dissociation below the *LAT*, whereas the latter has a major role above it (see Fig. 2.20).

The biochemical interactions between capillary blood and muscle cell for optimizing the O_2 supply to mitochondria during heavy exercise are summarized in Figure 2.34. As the blood transits the muscle from arteriole to venule, the capillary P_{O_2} decreases and oxyhemoglobin dissociates. As capillary P_{O_2} falls to its critical value, lactic acid increases in the cell. Capillary blood H^+ quickly increases because the lactic acid–producing cells generate additional CO_2 from HCO_3^- when buffering lactic acid. Although the intracellular buffering of lactic acid by HCO_3^- minimizes the change in cell pH, it acidifies blood more quickly than if a non-HCO_3^- buffer neutralized the cellular lactic acidosis because of its diffusibility and solubility. This is a most remarkable physiological mechanism because the Bohr effect would not be as great with any other buffer other than HCO_3^-. Thus, the lactic acidosis–facilitated oxyhemoglobin dissociation ensures a higher blood O_2 extraction and thereby a higher maximal $\dot{V}o_2$ than would otherwise be possible.

Plasma Electrolyte Concentrations

Plasma Sodium and Chloride

During an incremental exercise test, arterial plasma sodium and chloride concentrations and total cation and anion concentrations increase above—but not below—the *LT* (see Fig. 2.35).[146] This suggests that extracellular water volume has decreased. Because the total exercise duration was only about 15 minutes, with only a few minutes of heavy exercise, it is unlikely that the extracellular water loss is due to sweating. Rather, the most likely cause of the extracellular water loss above the *LT* is a shift of water from the extracellular to the muscle intracellular space. This will be caused by the increase in muscle intracellular osmolality resulting from the increase in intracellular lactate and other byproducts of metabolism in equilibrium with lactate. This increase in intracellular osmotic force must occur with obligatory water flux into cells to balance the altered osmotic forces associated with increased lactate production.

Plasma Potassium Concentration

Change in plasma K^+ differs from Na^+ and Cl^- ions in that its concentration starts to increase below the *AT* within 5 seconds after the start of exercise (see Fig. 2.25). However, its rate of increase is faster above the *AT*.[147] The timing of the K^+ release from cells, with linkage to new HCO_3^- efflux from the contracting muscle, suggests that the mechanism of K^+ release is linked to the hydrolysis of PCr. When the latter is hydrolyzed, it creates an alkaline reaction in the cell. Thus, strong cations are in relative excess in the cell compared with the extracellular fluid. Because K^+ is the primary intracellular cation, it would be the cation that would leave the cell to balance the charge across the cell membrane. It has been shown that the anion balancing the K^+ released during early exercise is HCO_3^-.[147]

Hemoconcentration

The fact that hemoconcentration occurs when humans perform exercise has been described in a number of studies.[8,67,121] In certain animals, this is due to splenic contraction, but this does not appear to be the mechanism in humans. Jung et al.[66] found that the hemoconcentration occurs primarily during exercise above the *LT*, as illustrated in Figure 2.36. The clue for the mechanism of hemoconcentration resides in the observation that the concentration of the total extracellular cations and anions increases above the *LT* (see Fig. 2.35). Because the cell osmolality must increase above the *LT*, extracellular fluid would move into cells rich in lactate. The shrinkage of the extracellular fluid would increase the red cell and therefore the arterial O_2 concentration, providing more O_2 per mL of blood flow at exercise levels above the *LT* (see Fig. 2.36). This could benefit the subject during exercise in which the O_2 supply limits exercise performance.

Metabolic Intermediaries

In muscle biopsy studies performed immediately at the cessation of exercise in humans, Katz and Sahlin[71] found that cellular alpha-glycerol phosphate increased in proportion to the increase in lactate. Muscle cell pyruvate and alanine also increased above the *LT*. These changes are most likely secondary to the change in cytosolic redox state and the accelerated rate of muscle glycolysis, which takes place above the *LT*.

$\dot{V}O_2$ and $\dot{V}CO_2$ Kinetics: Constant Work Rate Exercise

Figure 1.4 shows the typical onset responses of $\dot{V}O_2$ and $\dot{V}CO_2$ for moderate-intensity exercise (i.e., exercise that

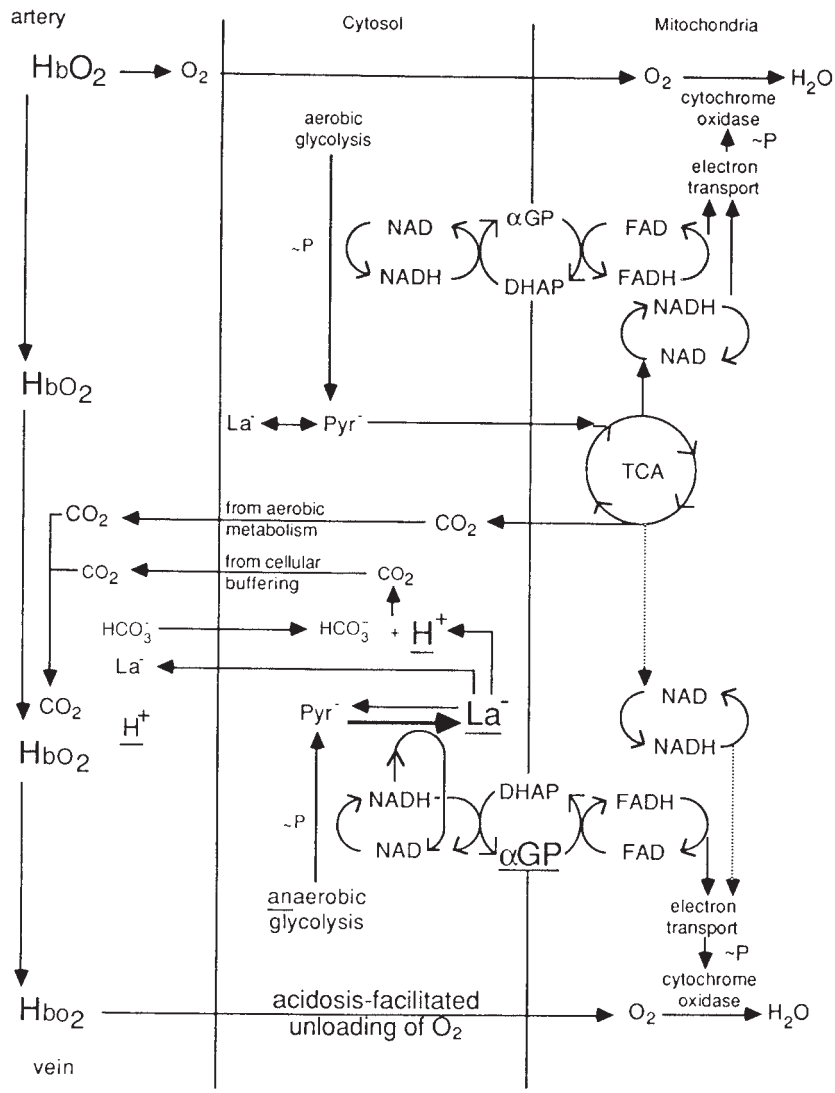

FIGURE 2.34. Scheme of changing capillary oxyhemoglobin (HbO_2) saturation during blood transit from artery to vein during heavy-intensity exercise. At the arterial end of the capillary, HbO_2 dissociates primarily due to decrease in P_{O_2}. Glycolysis proceeds aerobically, without an increase in lactate (La^-), because mitochondrial membrane redox shuttles (e.g., dihydroxyacetone acetone phosphate, DHAP) regulate cytosolic redox state $[NADH+H^+]/NAD^+$, abbreviated NADH/NAD. The primary substrate for the tricarboxylic acid (TCA) cycle is pyruvate (Pyr). As pyruvate is metabolized in the mitochondria, protons and electrons flow through the electron transport chain to O_2, generating high-energy phosphate (*~P*) with H_2O and CO_2 as by-products. As blood reaches the venous end of the capillary, where P_{O_2} becomes critically low, mitochondrial membrane redox shuttle fails to reoxidize NADH to NAD^+ at an adequate rate. Thus, the $NADH/NAD^+$ ratio increases. Accordingly, pyruvate is converted to La^-, and DHAP is converted to glycerol 3-phosphate (G3P) in proportion to the change in cell redox state.[71] The effect is an increase in cell La^- with a stoichiometric increase in H^+. The latter is immediately buffered by HCO_3^- in the cell. Decreasing cellular HCO_3^- and increasing cellular La^- results in intracellular–extracellular La^- and HCO_3^- exchange (see Fig. 2.2). Simultaneously, CO_2 formed during intracellular buffering, leaves the cell. The sum of aerobically and anaerobically produced CO_2 (from buffering), along with decreasing blood HCO_3^- (see Fig. 2.21), further acidifies the capillary blood toward the venous end of the capillary, enhancing dissociation of HbO_2 (Bohr effect). This acidosis-facilitated dissociation of HbO_2 allows aerobic metabolism to proceed at a rate proportional to the rate of acidification of blood, without a further reduction in capillary P_{O_2}. (Modified from Wasserman K. Coupling of external to cellular respiration during exercise: the wisdom of the body revisited. *Am J Physiol.* 1994;266:E519–E539.)

does not engender a lactic acidosis) and heavy-intensity exercise (i.e., exercise that results in a sustained lactic acidosis). The patterns of gas exchange differ between exercise performed at work rates with and without lactic acidosis, making it possible to discern if the work rate is above or below the *LAT* from gas exchange measurements at the airway.[23,141] In the absence of lactic acidosis, $\dot{V}O_2$ in healthy subjects reaches a steady state by 3 minutes, whereas $\dot{V}CO_2$ increases more slowly, reaching a steady state in about 4 minutes. In the steady state of moderate-

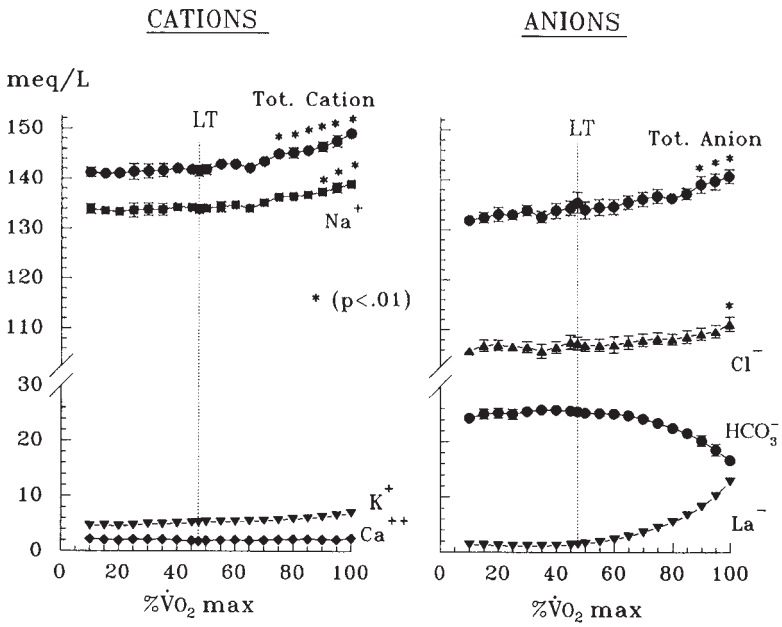

FIGURE 2.35. Change in arterial plasma Na^+, K^+, Ca^{++}, and total measured cations **(left panel)** and Cl^-, HCO_3^-, La^-, and total measured anions **(right panel)** during a progressively increasing exercise test to maximum level tolerated. Data are the average for 10 normal adult subjects. The *vertical bars* on points are the standard errors of the means. The *vertical line* passing through all the curves is the average lactate threshold (*LT*).

intensity exercise, $\dot{V}CO_2$ is slightly lower than $\dot{V}O_2$ (see Fig. 2.37A),—that is, the metabolic substrate respiratory quotient is less than 1.0. For constant-load exercise above the *LAT* (see Fig. 2.37B, C), $\dot{V}CO_2$ generally exceeds $\dot{V}O_2$, with the excess CO_2 being generated when HCO_3^- buffers lactic acid (see Fig. 2.37G–I).

Figure 2.37D–F illustrates that $\dot{V}CO_2$ kinetics are slow relative to $\dot{V}O_2$ within the first minute of exercise.

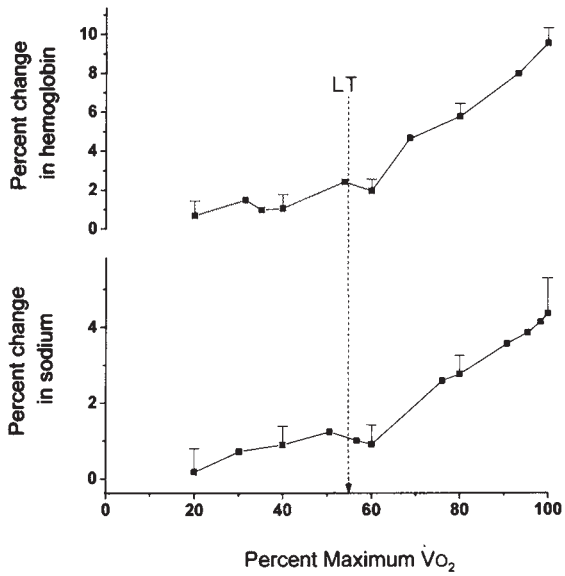

FIGURE 2.36. Change in arterial hemoglobin, and plasma sodium concentration during progressively increasing work rate exercise. Data are the average for 10 normal adult subjects. The *vertical bars* on points are the standard errors of means. The *vertical line* passing through the curves is the average lactate threshold (*LT*) for the group. The standard deviation of the *LT* is ±4.8%.

This slow CO_2 output relative to O_2 uptake during this early exercise period is accounted for in part by the early increase in blood HCO_3^- and K^+, described earlier.[147]

For exercise performed above the *AT*, the overall $\dot{V}O_2$ kinetics are slow compared with exercise performed below the *AT*, and a steady state in $\dot{V}O_2$ is often not reached before the subject fatigues (see Fig. 2.6). In contrast to $\dot{V}O_2$ kinetics, the general profile of the $\dot{V}CO_2$ response does not change appreciably during above-*AT* exercise (Fig. 2.38), and, usually after 1 minute of such exercise, $\dot{V}CO_2$ exceeds $\dot{V}O_2$ (see Figs. 2.37 and 2.38), with the magnitude depending on the rate of lactate increase.[23,175] The extra CO_2 generated by heavy-intensity exercise can be accounted for by the CO_2 produced as HCO_3^- buffers the H^+ from lactic acid, and to a lesser degree, by CO_2 unloading from body stores due to hyperventilation if $PaCO_2$ is decreased (see Figs. 2.2 and 2.30).

Ventilatory Drive above the Anaerobic (Lactic Acidosis) Threshold

Ventilation tracks the acidity added to the blood as a result of metabolism. Up to the *LAT*, $\dot{V}E$ tracks $\dot{V}CO_2$ with each CO_2 molecule being exhaled representing an H^+ ion. H^+ ion in the arterial blood is in the nanomolar range, while its production is in the millimolar range each minute—some million times greater. The addition of CO_2 from the HCO_3^- buffering of lactic acid, as well as the reduction in plasma HCO_3^- concentration, add acid equivalents to the blood. The ventilatory control mechanisms are stimulated to provide levels of ventilation that continue to increase during exercise as long as the arterial pH remains reduced. The proposed control mechanisms are discussed in greater detail later in this chapter. The magnitude of

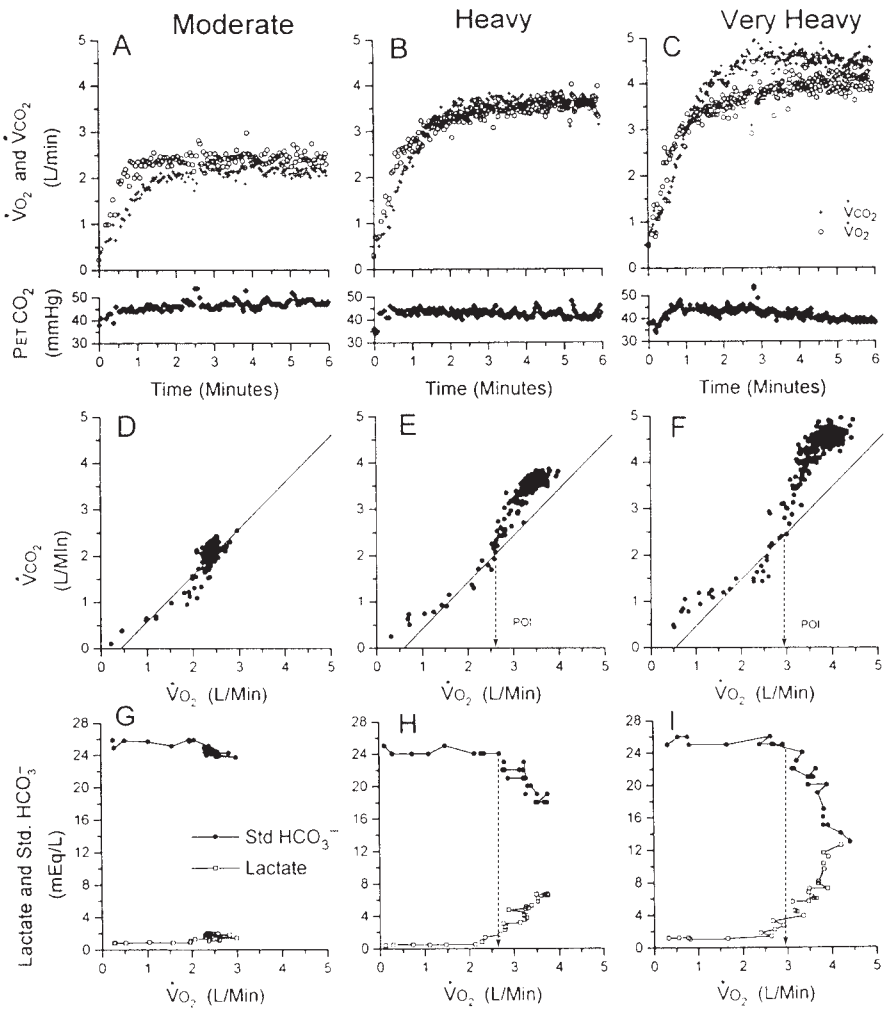

FIGURE 2.37. O_2 uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), and $P_{ET}CO_2$ plotted as a function of time **(A–C)** and $\dot{V}CO_2$, arterial lactate HCO_3^-, and standard (Std) HCO_3^- are plotted as a function of $\dot{V}O_2$ **(D-I)** for constant work rate tests of moderate, heavy, and very heavy work intensity. Steepening of $\dot{V}CO_2$ relative to $\dot{V}O_2$ (*arrow* in **E** and **F**, POI [point of inflection]) occurs simultaneously with the increase in lactate and decrease in HCO_3^- (*arrow* in **H** and **I**), reflecting the buffering of the lactic acid by HCO_3^-. (Modified from Stringer WW, Wasserman K, Casaburi R. The $\dot{V}CO_2/\dot{V}O_2$ relationship during heavy, constant work rate exercise reflects the rate of lactate accumulation. *Eur J Appl Physiol.* 1995;72:25–31.)

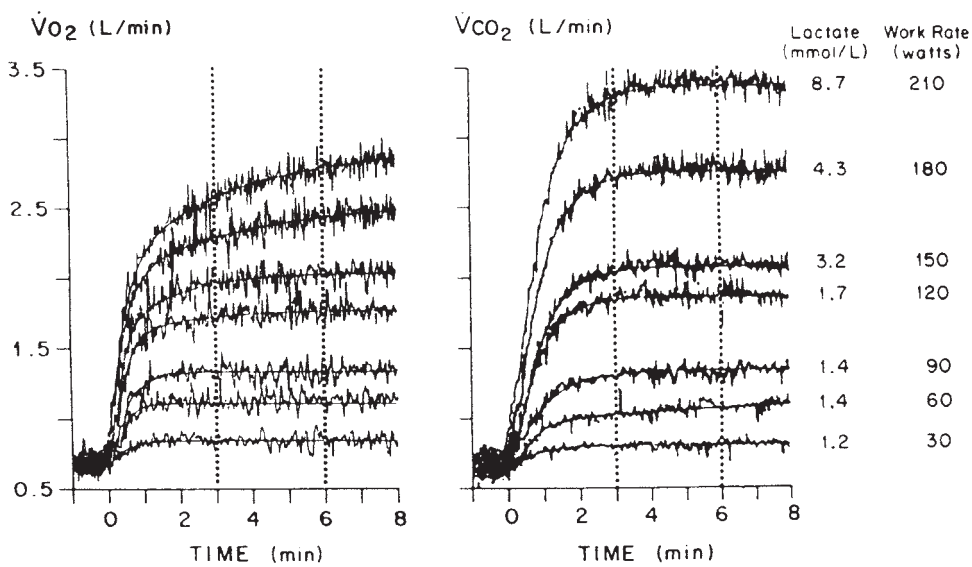

FIGURE 2.38. O_2 uptake ($\dot{V}O_2$) and CO_2 output ($\dot{V}CO_2$) as related to time at seven different levels of work for a healthy subject. The three lowest work rates are below the subject's lactic acidosis threshold (*LAT*), whereas the four highest work rates are above it. The $\dot{V}O_2$ continues to rise for the four work rates above the *LAT*, the rate of rise being more marked the higher the work rate. In contrast, the $\dot{V}CO_2$ kinetics are relatively unchanging, reaching a constant level by 3 to 4 minutes in all seven tests. (Modified from Casaburi R, Barstow TJ, Robinson T, et al. Influence of work rate on ventilatory and gas exchange kinetics. *J Appl Physiol.* 1989;67:547–555.)

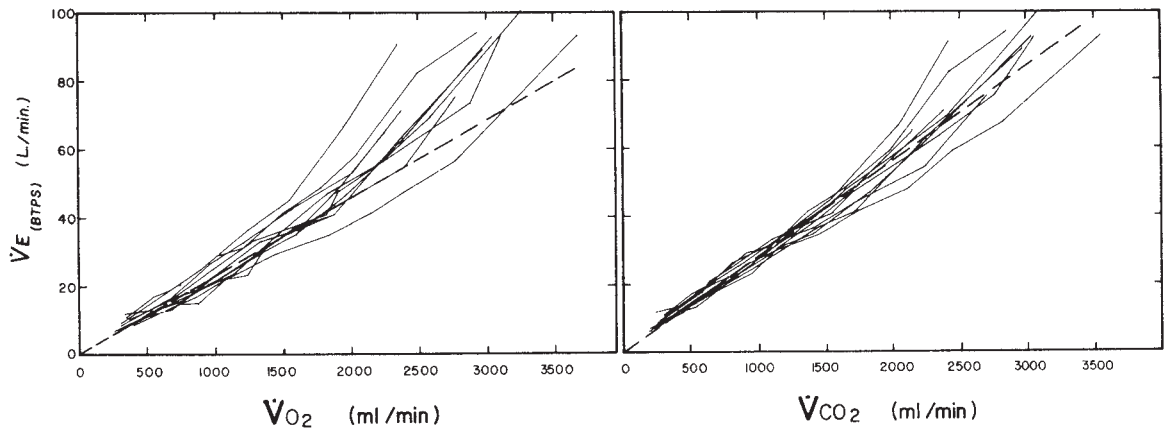

FIGURE 2.39. Relationship between minute ventilation ($\dot{V}_E$) and oxygen uptake ($\dot{V}O_2$), and CO_2 output ($\dot{V}CO_2$) in 10 normal subjects. The curvilinear increase in ventilation at high metabolic rates reflects respiratory compensation for the metabolic acidosis. The reduced dispersion noted in the correlation between $\dot{V}_E$ and $\dot{V}CO_2$, as compared with $\dot{V}_E$ and $\dot{V}O_2$, reflects the functional dependence of ventilation on arterial CO_2 or H^+ regulation. The greater dispersion of the $\dot{V}_E$ versus $\dot{V}O_2$ slopes reflects differences in respiratory quotient among the subjects. (From Wasserman K, VanKessel AL, Burton GG. Interaction of physiological mechanisms during exercise. *J Appl Physiol.* 1967;22:71–85, with permission.)

the added ventilatory drive is illustrated in Figure 2.39 and Table 2.3.

Although net lactic acid production, through its H^+, stimulates breathing that causes hyperventilation, it might also induce dyspnea in the ventilatory-limited subject. However, the lactic acidosis might provide more benefit than hindrance to the normal subject during the performance of high-intensity exercise because of the following:

1. The facilitation of oxyhemoglobin dissociation through the Bohr effect, thereby allowing increased oxygen extraction from blood
2. The increased arterial O_2 content resulting from the hemoconcentration that takes place above the *AT*
3. The regional vasodilatation caused by the regional acidosis
4. The hyperventilation-induced increase in PaO_2, which can maintain or even increase PaO_2 (particularly important to the subject performing exercise at high altitude)

Table 2.3

Increase in Blood Lactate (Δ Lactate), $\dot{V}_E$, and Heart Rate at 6 Minutes of Work Rate of 200 W

Subject	Δ Lactate (mmol/L)	$\dot{V}_E$ (L/min)	Heart rate (beats/min)
1	1.9	60	156
2	2.7	81	163
3	5.0	79	151
4	5.1	85	153
5	9.7	151	186

Catecholamines

The plasma catecholamines increase at work rates above the *LT*.[158] The catecholamine increases might represent a cardiovascular compensatory mechanism for the anaerobic stress. Similar changes are reported to take place, but at lower work rates, in patients with chronic heart failure.[33,108]

Rate–Pressure Product

The product of heart rate and systolic pressure increases during exercise, becoming steeper above the *AT*.[109] The increasing catecholamine levels likely contribute to the steepening in the rate–pressure product. The steeper rate–pressure product above the *AT* might be a mechanism that serves to enhance O_2 delivery to muscle when there is an imbalance between O_2 demand and O_2 supply.

METABOLIC-CARDIOVASCULAR-VENTILATORY COUPLING

Sources of Adenosine Triphosphate Regeneration Reflected in $\dot{V}O_2$ and $\dot{V}CO_2$ Kinetics

A scheme describing the gas transport mechanisms for coupling cellular (internal) to pulmonary (external) respiration is shown in Figure 1.3. When exercise is initiated, high-energy phosphate bonds of preexisting ATP are split to support the immediate energy requirements of contracting muscle. The resulting ADP is rapidly rephosphorylated to ATP from creatine phosphate and the conversion of substrate energy to chemical energy (~P), primarily in muscle mitochondria. Creatine ~P concentration rapidly decreases in proportion to the

work rate performed,[89] and its concentration remains reduced as the work is sustained, returning to the pre-exercise resting level within the first few minutes of recovery.[173] Experimental evidence suggests that the increases in concentration of creatine, inorganic phosphate, and ADP in the muscle stimulate oxidative phosphorylation, thereby replenishing ATP.[27,28] This keeps the ATP relatively constant during exercise as the metabolic requirement approaches the subject's maximal exercise capacity. Only as maximal work rates are approached does muscle ATP concentration often start to decrease and the less phosphorylated adenosine compounds increase.[22]

Although the mitochondria are the major site of ATP regeneration, two anaerobic sources of ATP are used during exercise, with the magnitude depending on the work level and the subject's fitness. These are the factors that determine the $\dot{V}O_2$ kinetics and hence the O_2 deficit. The kinetics of $\dot{V}O_2$ are dependent on an adequate circulatory coupling of external respiration to muscle respiration (see Fig. 1.3). The contributions of the two anaerobic sources for regenerating ATP—splitting of PCr and anaerobic glycolysis—depend on how effectively the circulation couples external to cellular respiration. The two anaerobic mechanisms of ATP regeneration operate only transiently during moderate and heavy-intensity exercise and need to be restored by aerobic (O_2-requiring) mechanisms in recovery. These mechanisms account for a major part of the O_2 debt.

Of the two anaerobic sources of ~P that contribute to exercise bioenergetics (see Fig. 1.3), the first in time sequence is that derived from the hydrolysis of intramuscular PCr.[15] Because the circulation cannot respond as quickly as muscle contraction can be initiated, muscle PCr serves as a source of ~P to regenerate muscle ATP at the myofibril early during the exercise. This source of ~P is immediately available at the start of exercise, but it is limited in quantity and is not regenerated until the return to resting state. Its contribution during exercise is complete by the time $\dot{V}O_2$ reaches a steady state.[7,112]

PCr splitting also affects CO_2 output. When PCr is split, the cell pH turns alkaline because PCr, an acid molecule at cell pH, produces neutral creatine and a mix of dibasic and monobasic phosphate with a pK (6.8) close to the pH of the cell.[174] The resulting alkalinization of the cell loses negative charges. Thus, the cations (K^+) in the cell become in excess.[147] CO_2, hydrated to H_2CO_3, dissociates into HCO_3^- and H^+. The alkaline cell takes up the H^+, while the HCO_3^- serves to balance the positive charge of K^+ liberated when PCr loses its negative charge when splitting (see Fig. 2.26). The net effect of this reaction is the fixation of metabolic CO_2 as HCO_3^- during this early period of exercise. The increase in HCO_3^- balancing the K^+, as it leaves the myocyte, is reflected in the exercising muscle venous effluent.[147] Thus, femoral vein pH, HCO_3^-, and K^+ increase concurrently (see Fig. 2.25).

Femoral vein P_{CO_2} does not increase during this early period of exercise, despite an increase in $\dot{V}O_2$ and decrease in femoral vein P_{O_2}, because metabolic CO_2 is simultaneously fixed as HCO_3^- (see Fig. 2.25). Consequently, the respiratory exchange ratio (R) decreases during the first minute of exercise (Figs. 2.25 and 2.40). Chuang et al.[30] pointed out that about two-thirds of the metabolic CO_2 retained in the body during this early period of exercise accounts for the slow increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$ and the decrease in R during the first minute of exercise (see Fig. 2.40). The remainder is attributable to the

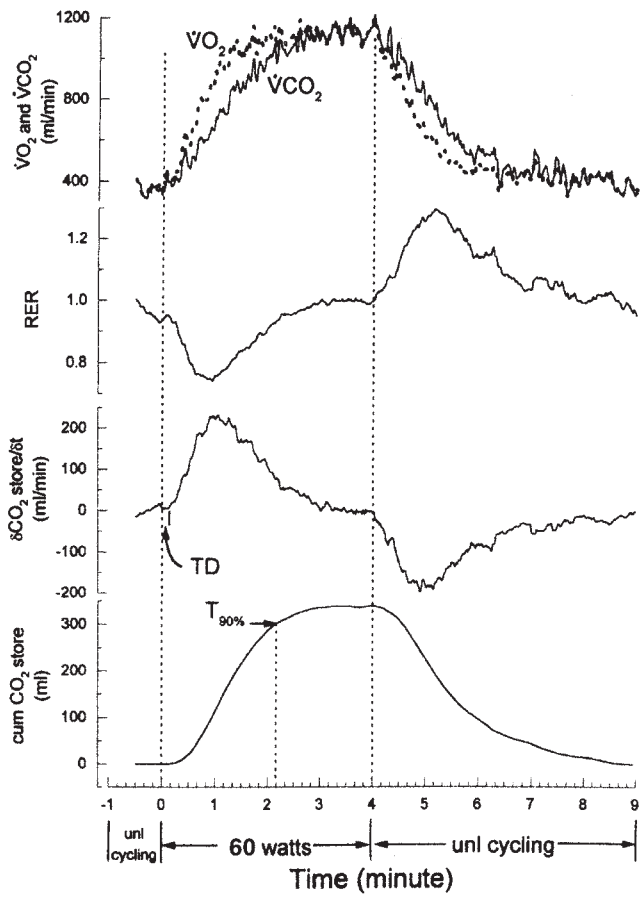

FIGURE 2.40. $\dot{V}o_2$ and $\dot{V}co_2$ **(top)**, respiratory exchange ratio (RER) **(second from top)**, rate of change in CO_2 **(third from top)**, and the cumulative change in CO_2 store **(bottom)** in response to a 4-minute 60-W constant work rate upright leg cycling exercise, starting at zero time from unloaded cycling, followed by 5-minute unloaded cycling recovery period. The data are second-by-second averages of four replicate tests. TD = time delay for increase in CO_2 stores to be reflected in lung gas exchange; $T_{90\%}$ = time for completion of 90% of CO_2 stores. (From Chuang M-L, Ting H, Otsuka T, et al. Aerobically generated CO_2 stored during early exercise. *J Appl Physiol.* 1999;87:1048–1058, with permission.)

increase in CO_2 dissolved in tissues when tissue P_{CO_2} increases, and to the increase in CO_2 in venous blood due to the Haldane effect (increased binding of CO_2 due to decreasing venous oxyhemoglobin saturation). The increase in CO_2 content in venous blood, other than that due to the Haldane effect, is not part of this component because it is closely offset by the unmeasured O_2 consumed from the venous blood O_2 stores during the same period of exercise.

The second anaerobic mechanism, the anaerobic degradation of glycogen or glucose to lactate, starts after some 30 seconds of exercise if the circulatory delivery of O_2 is inadequate.[147] This source of ATP is particularly important when the energy requirement exceeds the sum of PCr splitting and the aerobic regeneration of ~P. This is an exercise intensity defined as being above the subject's *AT* (see pathway B of Fig. 2.1).[12,154] The *AT* should therefore be a particularly important index of the work rate that can be sustained aerobically.[142]

Cardiovascular Coupling to Metabolism: Muscle Oxygen Supply

Cardiac output increases at the start of exercise in the upright position by increasing stroke volume and heart rate. Heart rate increases initially as vagal tone decreases with a subsequent increase in sympathetic stimulation. Stroke volume increases due to increased venous return resulting from the compression of veins by contracting muscles and decreased intrathoracic pressure accompanying increased depth of breathing in addition to increased cardiac inotropy.[116] As exercise continues, further increases in cardiac output are achieved predominantly by increasing heart rate, with stroke volume remaining relatively constant.

The pulmonary vascular bed dilates at the start of exercise in concert with the increase in right ventricular output and pulmonary artery pressure. This dilatation results in the perfusion of previously unperfused and underperfused lung units in the normal pulmonary vascular bed, accounting for the fact that there is only a small increase in pulmonary artery pressure as pulmonary blood flow increases in the normal lung. A low pulmonary vascular resistance is essential for the normal exercise response of the left ventricle. Without it, the weakly muscled right ventricle could not readily pump the venous blood through the pulmonary circulation to the left side of the heart at a rate fast enough to achieve the increase in cardiac output needed to support cellular respiration.

Because the proportional increase in cardiac output is less than that of $\dot{V}_{O_2}$, the extraction of O_2 from, and addition of CO_2 to, the muscle capillary blood must increase. Muscle blood flow increases appropriate to its metabolic activity.[52] Because of the falling capillary P_{O_2} and the Bohr effect, it is possible to extract 75% to 85% of the O_2 going through the capillary bed of maximally working muscle. The oxygen supply to the muscle cells is dependent on five factors:

1. Cardiac output
2. Distribution of perfusion to the tissues in need of O_2
3. Partial pressure profile of O_2 in the capillary blood
4. Hemoglobin concentration
5. Hemoglobin's affinity for O_2

As previously stated, the transport of O_2 from blood to mitochondria is dependent on maintaining an adequate diffusion gradient for O_2 as the blood travels through the contracting muscle. The P_{O_2} gradient between blood and cell is high at the arterial end of the capillary but decreases as the blood approaches the venous end of the capillary, depending on the O_2 flow–metabolic rate ratio (Fig. 2.15). The critical capillary P_{O_2} limiting diffusion during exercise appears to be about 20 mm Hg.[2,50,77,91,126,133]

Cardiac Output

The cardiac output obviously must play a key role in the O_2 supply to the cells. At the start of exercise in the upright posture, stroke volume increases virtually immediately,[85] with the magnitude being dependent on the relative degree of the individual's fitness, age, and size.[116] In an exceptionally fit young person, the stroke volume can increase by as much as 100%; the increase is much smaller in less fit and elderly people. After the initial increase in stroke volume that takes place at low levels of exercise, cardiac output increase comes about predominantly by increasing heart rate; that is, heart rate usually increases linearly with $\dot{V}_{O_2}$ (see the case studies of normal subjects in Chapter 10). A method for estimating the stroke volume noninvasively from the $\dot{V}_{O_2}$–heart rate relationship during progressively increasing exercise is presented in Chapters 3 and 9.

Distribution of Peripheral Blood Flow

During exercise, the fraction of the cardiac output diverted to the skeletal muscles increases, while the fraction perfusing organs such as the kidney, liver, and gastrointestinal tract decreases.[116] The increase in blood flow through the working muscles, and a small fraction through the skin to eliminate some of the heat generated during exercise, accounts for almost all of the increase in cardiac output that takes place during exercise. The mechanism by which blood flow is distributed during exercise depends on the response of the autonomic nervous system and local humoral control. The blood flow–metabolic rate relationship affects the level of local humoral factors, such as in-

creased [H^+], P_{CO_2}, [K^+], osmolarity, adenosine, temperature, nitric oxide, and P_{O_2}. These can act locally to regulate regional blood flow according to its metabolic requirement.[41]

Arterial P_{O_2}

In the normal subject, arterial P_{O_2} (P_{aO_2}) is a function of mean alveolar P_{O_2} (P_{AO_2}). For an idealized lung (all lung units having the same ventilation–perfusion ratio and no diffusion impairment) where the gas exchange ratio is 0.8 and P_{ACO_2} is equal to 40 mm Hg, P_{AO_2} would equal approximately 100 mm Hg at sea level. Reductions in P_{aO_2} relative to the ideal P_{AO_2} are due to one or more of the following mechanisms: a right-to-left shunt; O_2 diffusion disequilibrium at the alveolar–capillary interface; or maldistribution of alveolar ventilation ($\dot{V}A$) with respect to lung perfusion ($\dot{Q}$). Normal young adults have a P_{aO_2} of about 90 mm Hg (Fig. 2.41) with a $P(A-a)O_2$ of approximately 10 mm Hg during exercise at sea level.[148] This difference between the alveolar and arterial P_{O_2} can be attributed to a small right-to-left shunt (possibly the thebesian blood vessels in the heart and the bronchial circulation) and the lack of total uniformity of $\dot{V}A/\dot{Q}$ within the lungs. In very highly fit subjects, diffusion impairments have also been described at very high work rates with $P(A-a)O_2$ exceeding 30 mm Hg.[38]

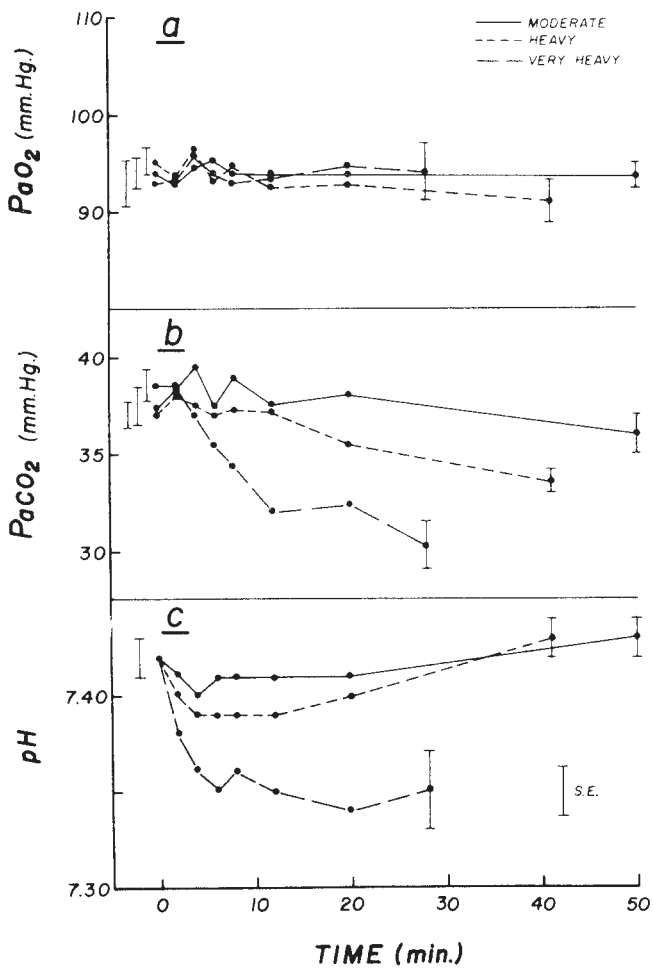

FIGURE 2.41. Effect of prolonged constant work rate exercise of moderate, heavy, and very heavy work intensity on arterial blood gases and pH. Each point is the average of 10 subjects. (From Wasserman K, VanKessel AL, Burton GG. Interaction of physiological mechanisms during exercise. *J Appl Physiol.* 1967;22:71–85, with permission.)

Oxyhemoglobin Dissociation in Tissue

Oxyhemoglobin dissociation and the essential role played by the Bohr effect on oxygen extraction were discussed previously (see Figs. 2.20 and 2.34). Increased levels of 2,3-diphosphoglycerate (2,3-DPG) also contribute to a right-shifted oxyhemoglobin dissociation curve, but this occurs simultaneous with the lactic acidosis and therefore their effects are difficult to separate. Altered hemoglobin affinity for O_2, as seen with either congenital or acquired abnormal hemoglobin, may impair muscle O_2 supply. This might be due to either the effect on the arterial O_2 content or on the P_{50} of the hemoglobin (the partial pressure of O_2 in the blood when active hemoglobin is 50% saturated with O_2). Genetic defects causing a shift in the oxyhemoglobin dissociation curve to the left (low P_{50}) can impair O_2 extraction by the exercising muscle, since there is a floor P_{O_2} for O_2 diffusion. This will reduce $\dot{V}O_2$. It might also induce polycythemia in compensation.[21]

Hemoglobinopathies that shift oxyhemoglobin dissociation curve to the right (high P_{50}) allow O_2 to unload from hemoglobin more readily and are generally associated with anemia.[21] Shifts in P_{50} are common even in normal subjects. A rightward shift resulting from acidosis, increased temperature, or high levels of 2,3-DPG favors diffusion of O_2 from the capillaries into the mitochondria. This contrasts with the leftward shift resulting from alkalosis, carbon monoxide toxicity, or low 2,3-DPG concentrations, where the O_2 diffusion gradient is reduced.

Hemoglobin and Arterial Oxygen Content

The arterial O_2 content depends on the arterial P_{O_2} and hemoglobin concentration that is free to take up O_2. Thus, anemia, resulting in a decreased blood O_2 content, can compromise the supply of O_2 to the tissues during exercise. Hemoglobin that is inactive (methemoglobin) or has carbon monoxide on the O_2 binding sites (as in cigarette smokers) will also result in a reduced O_2 content. All of these conditions will result in a more rapid decrease in capillary P_{O_2} than normal, and the minimal capillary P_{O_2} needed for diffusion will be reached at a lower metabolic rate than if all of the hemoglobin were available for O_2 transport. In the presence of anemia or increased concen-

tration of inactive hemoglobin, the blood flow–metabolic rate ratio of the muscle ($\dot{Q}m/\dot{V}O_2m$) must increase to enable a given level of cellular respiration.

Ventilatory Coupling to Metabolism

To remove the CO_2 produced during muscle respiration, the muscles must be perfused by arterialized blood, with a PCO_2 low enough to allow the CO_2 produced by cellular respiration (see Fig. 1.3) to diffuse into the muscle blood supply at a sufficiently rapid rate. To rearterialize the blood, ventilation must increase appropriately to eliminate the H^+ equivalents from CO_2 and H^+ created with lactate, while simultaneously replenishing the O_2 consumed. Minute ventilation ($\dot{V}E$) normally increases at a rate required to remove the CO_2 added to the capillary blood by metabolism while minimizing the increase in arterial H^+ concentration (achieving H^+ homeostasis). From rest to the *AT*, $\dot{V}E$ generally increases so precisely that arterial PCO_2 and H^+ increase by only approximately 2 mm Hg and 2 nmol/L, respectively.[125,129] Above the *AT*, the lactic acidosis stimulates ventilation further, thereby decreasing $PaCO_2$ and constraining the fall in pH.

At low and moderate work rates, the tidal volume–breathing rate pattern for increasing ventilation is primarily achieved by an increase in tidal volume and, to a lesser degree, breathing frequency (Fig. 2.42). The latter increases to a greater extent at work rates above the *AT*.

Carbon Dioxide Elimination

CO_2 production increases during exercise because of the increase in metabolic activity of the exercising muscles. The amount of CO_2 generated by this process is related to O_2 consumption by the RQ of the muscle substrate. As described earlier and illustrated in Figures 2.37 and 2.38, a substantial amount of additional CO_2 is derived from CO_2 stores when bicarbonate buffers lactic acid generated above the *AT*. CO_2 from stores is also added to the expired gas when the ventilatory control mechanism compensates for the lactic acidosis by hyperventilation. In contrast to muscle oxygen supply, the actual cardiac output needed for CO_2 elimination is less precise; CO_2 output is regulated by alveolar ventilation and thereby arterial CO_2 content (Fig. 2.43). The cardiac output does determine the venous-arterial CO_2 content difference $[C(a-\bar{v})CO_2]$ for a given metabolic (exercise) activity.

Aside from hemoglobin concentration, the venous CO_2 content for a given venous PCO_2 is dependent on changes in buffer base and O_2 content (Christiansen-Douglas-Haldane effect).[29] The latter changes most over the lower work rate range (below the *AT*). The former changes most

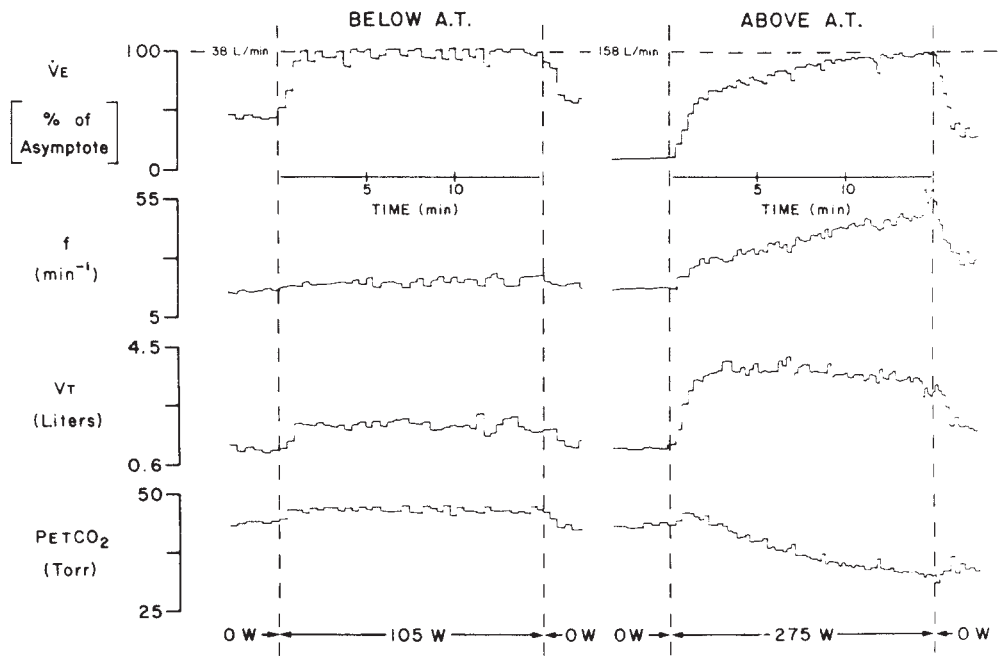

FIGURE 2.42. Minute ventilation ($\dot{V}E$) plotted as percentage of its asymptotic value, tidal volume (VT), breathing rate (f), and end-tidal PCO_2 ($PETCO_2$) for exercise below and above the anaerobic threshold in the same subject. The absolute values of minute ventilation are shown to the left of the *vertical dashed line* at the transition from unloaded cycling (0 W) to the indicated work rate. For the work rate below the anaerobic threshold, $\dot{V}E$, f, VT, and $PETCO_2$ reach constant values after several minutes. For the work rate above the anaerobic threshold, $\dot{V}E$ and f continue to increase, and $PETCO_2$ continues to decrease (without a significant change or slight decrease in VT), signifying the lack of a ventilatory steady state.

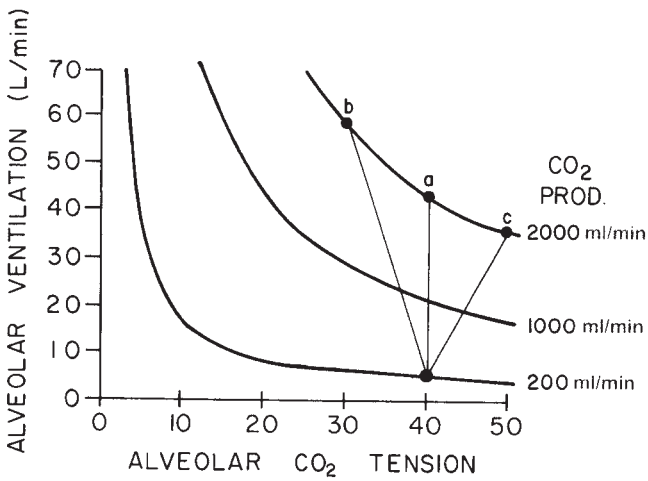

FIGURE 2.43. Effect of changing ideal alveolar P_{CO_2} during exercise on alveolar ventilation. The point on the CO_2 output isopleth of 200 mL/min represents the normal resting value. Points *a, b,* and *c* illustrate the alveolar ventilation for isocapnia, hypocapnia (–10 mm Hg), and hypercapnia (+10 mm Hg) for an exercise CO_2 output of 2,000 mL/min. (From Wasserman K. Breathing during exercise. *N Engl J Med.* 1978;298:780–785, with permission.)

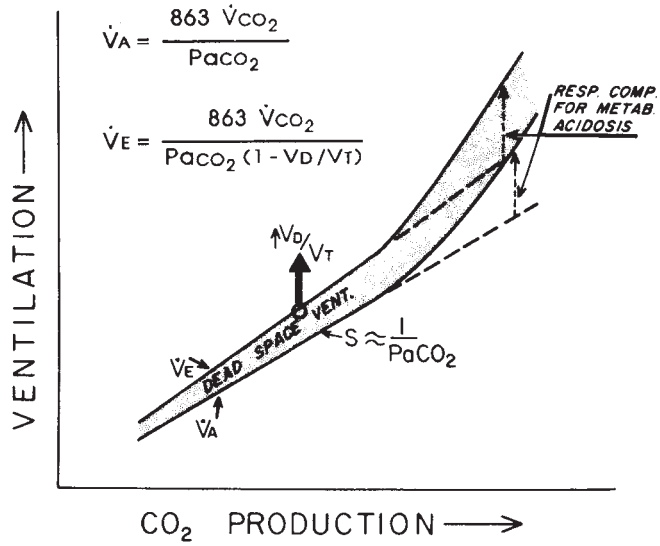

FIGURE 2.44. Factors that determine alveolar and minute ventilation ($\dot{V}_A$ and $\dot{V}_E$, respectively) during exercise are shown in the equations on top of the figure, and the relationships are shown as a graph. V_D/V_T is the ratio of the physiological dead space to the tidal volume, and *S* is the slope of the relationship, shown to be proportional to the reciprocal of the P_{aCO_2}. Respiratory compensation for the metabolic acidosis reduces the P_{aCO_2} value. As P_{aCO_2} decreases, the ventilatory curves become more steep. (Modified from Wasserman K. Breathing during exercise. *N Engl J Med.* 1978;298:780–785.)

over the heavy-intensity range (above the *AT*) due to HCO_3^- dissociation when buffering lactic acid.

Alveolar Ventilation

The quantity of alveolar ventilation ($\dot{V}_A$) required to clear a given amount of CO_2 from the blood ($\dot{V}CO_2$) per unit time depends on the CO_2 concentration (F_{CO_2}) in the alveolar gas ($F_{CO_2} = P_{CO_2}/P_B$), where P_B is the barometric pressure and P_{CO_2} is the ideal alveolar P_{CO_2} or arterial P_{CO_2}. Mass balance considerations dictate that, in an idealized lung, the ventilation–perfusion ratios of all lung units are the same, thereby making the CO_2 concentration the same in all alveolar spaces:

$$\dot{V}CO_2 = \dot{V}_A \times (P_{CO_2}/P_B)$$

or

$$\dot{V}_A = \dot{V}CO_2 \times (P_B/P_{CO_2})$$

This equation derives the theoretical alveolar ventilation ($\dot{V}_A$) required for maximally efficient lungs to regulate P_{CO_2} for a given $\dot{V}CO_2$. This important relation is plotted in Figure 2.43.

Dead Space Ventilation

Not all respired air ventilates the lungs effectively because some must ventilate the conducting airways, uninvolved in gas exchange, and some ventilate nonperfused or underperfused alveoli. The difference between the ideal alveolar ventilation and the total ventilation is the physiological dead space ventilation. Uneven ventilation relative to perfusion will result in a calculated increase in physiological dead-space/tidal-volume ratio (V_D/V_T) and an increase in $\dot{V}_E$ to clear a given volume of CO_2 from the lungs. Referring to Figure 2.43, given a P_{aCO_2} of 40 mm Hg composed of equal blood flow from two sets of acini yielding pulmonary venous P_{CO_2} values of 50 and 30 mm Hg, the actual total alveolar ventilation would be greater than ventilation from one homogeneous set of acini yielding the same P_{aCO_2}. Thus, with mismatching of ventilation to perfusion, the alveolar ventilation would be dominated by the lung unit with the low alveolar P_{CO_2} (i.e., high-$\dot{V}_A/\dot{Q}$ lung unit). The mixed expired CO_2 would be relatively low with mismatching of $\dot{V}_A/\dot{Q}$ as compared with that for an ideal lung in which $\dot{V}_A/\dot{Q}$ was perfectly matched.

See Figures 2.44 and 2.45 for illustrations of the effect of increase in V_D/V_T on $\dot{V}_E$, and the section "Physical Factors" later in this chapter for a quantification of the effect of increased dead space on the ventilatory response to exercise.

Acid–Base Balance

Because the end products of the bioenergetic pathways for generating ~P are acidic (i.e., the volatile carbonic and the nonvolatile lactic acid), ventilation must keep pace with the acid load if pH homeostasis of body fluids is to be preserved. Figures 2.23 and 2.46 show the acid–base changes in response to constant work rates of moderate,

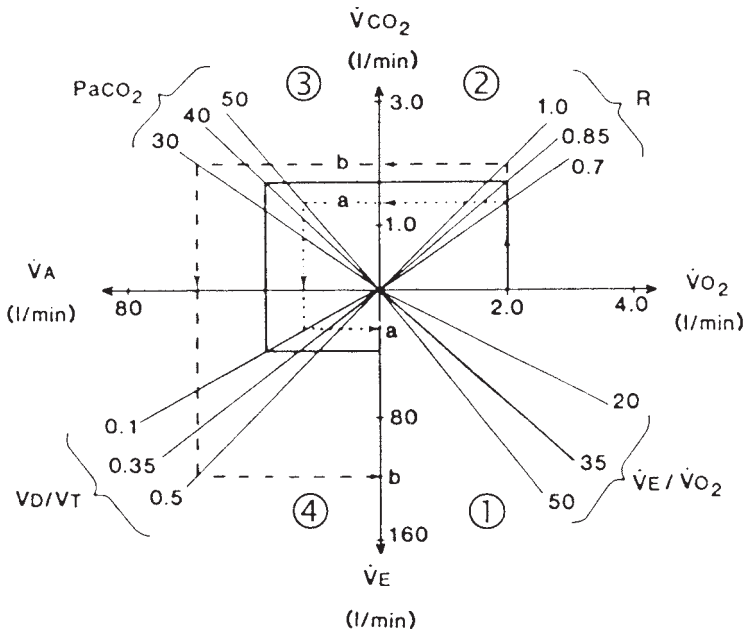

FIGURE 2.45. Graphic display of influence of respiratory exchange ratio (R), arterial partial pressure of CO_2 ($Paco_2$), and dead-space fraction of the breath (V_D/V_T) on ventilatory requirement ($\dot{V}_E$) for exercise with an O_2 consumption ($\dot{V}o_2$) of 2 L/min (STPD). The ventilatory requirement can be significantly altered from normal response (*solid line*), with a particular combination of determining variables leading to reduced (*arrow a*) or markedly increased (*arrow b*) $\dot{V}_E$. $\dot{V}_A$, alveolar ventilation. See text for equations showing how the parameter affects the variables in each quadrant. (Modified from Whipp BJ, Pardy RL. Breathing during exercise. In: *Handbook of Physiology,* Sect. 3, Vol. III. Bethesda, MD: American Physiological Society; 1985:605.)

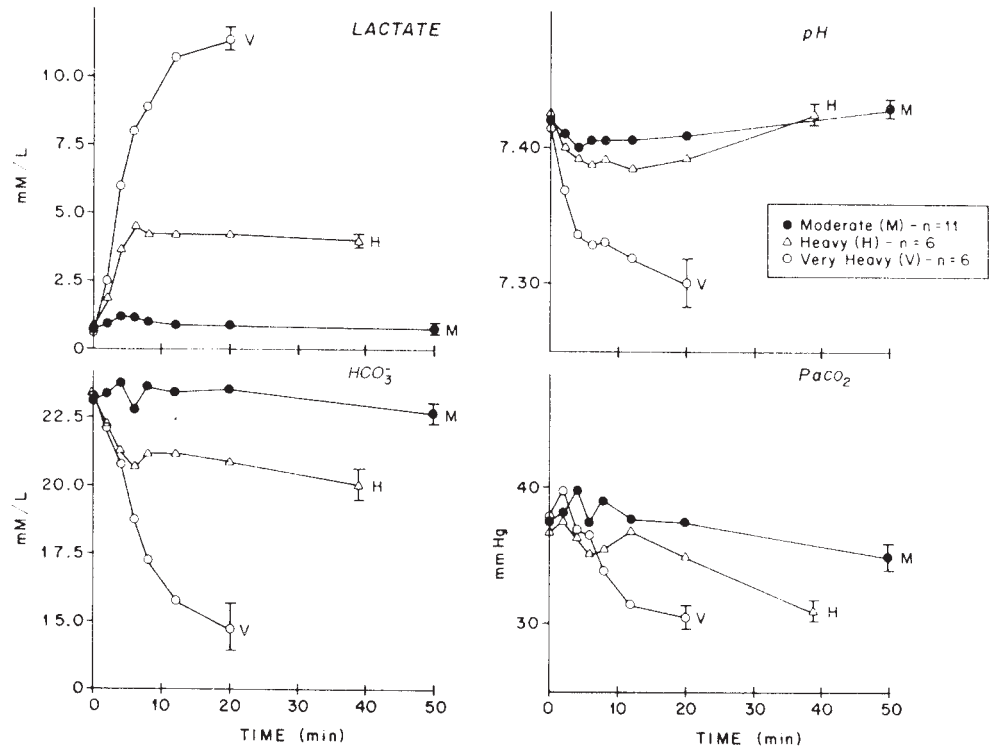

FIGURE 2.46. Time course of change in arterial lactate, bicarbonate, pH, and $Paco_2$ for moderate, heavy, and very heavy intensity constant-load cycle ergometer exercise. Moderate exercise intensity (n = 11) refers to an increase in arterial lactate level of less than 0.8 mmol/L above rest. Heavy exercise intensity (n = 6) refers to an arterial lactate increase at the end of exercise of 2.5 to 4.9 mmol/L above rest. Very heavy intensity exercise (n = 6) refers to a lactate increase of 7 mmol/L or greater above rest at the end of exercise. (Data computed from subjects previously reported in Wasserman K, VanKessel AL, Burton GG. Interaction of physiological mechanisms during exercise. *J Appl Physiol.* 1967;22:71–85.)

heavy, and very heavy intensity exercise. The ventilatory response does not overshoot the ventilation needed to regulate arterial pH. Characteristically, below the *AT*, the arterial pH is transiently regulated slightly below the resting level because of a small increase in Pa_{CO_2}.[155] For exercise above the *AT*, the acidosis becomes more marked because of the decrease in HCO_3^- caused by the net increase in lactic acid production and a relatively slow but increasing ventilatory response to the increase in arterial H^+ (see Fig. 2.42 and 2.46).

Change in Acid–Base Balance during Recovery

Because the change in pH is minimal during moderate-intensity exercise, recovery of pH following exercise is rapid (about 3 minutes), involving only maintaining Pa_{CO_2} at the resting set-point value (Fig. 2.47). At this exercise intensity, only the ventilatory excretion of the exercise-induced increase in CO_2 stores is required. If the exercise is of heavy or very heavy intensity, recovery of pH is slow because it is linked to the rate of regeneration of HCO_3^-, which, in turn, is dependent on the rate of lactate catabolism (see Fig. 2.47).[125,152]

Effect of Dietary Substrate

Oxygen Consumption

Table 2.4 shows the theoretical high-energy phosphate–gas exchange equivalents for pure carbohydrate and pure fatty acid substrate. Slightly more ATP is generated per molecule of O_2 utilized when carbohydrate is the substrate compared with fatty acids (~P:O_2 of 6.0 vs. 5.65, respectively). Consequently, steady-state $\dot{V}O_2$ should be slightly increased for a given work rate when fatty acids are the predominant substrate. This is demonstrated by the experiment shown in Fig. 2.48 (left panel). $\dot{V}O_2$ was measured during constant work rate cycle ergometry after the subject consumed a high-carbohydrate diet for 3 days and a high-fat diet for a similar duration. The $\dot{V}O_2$ is higher when the work task is

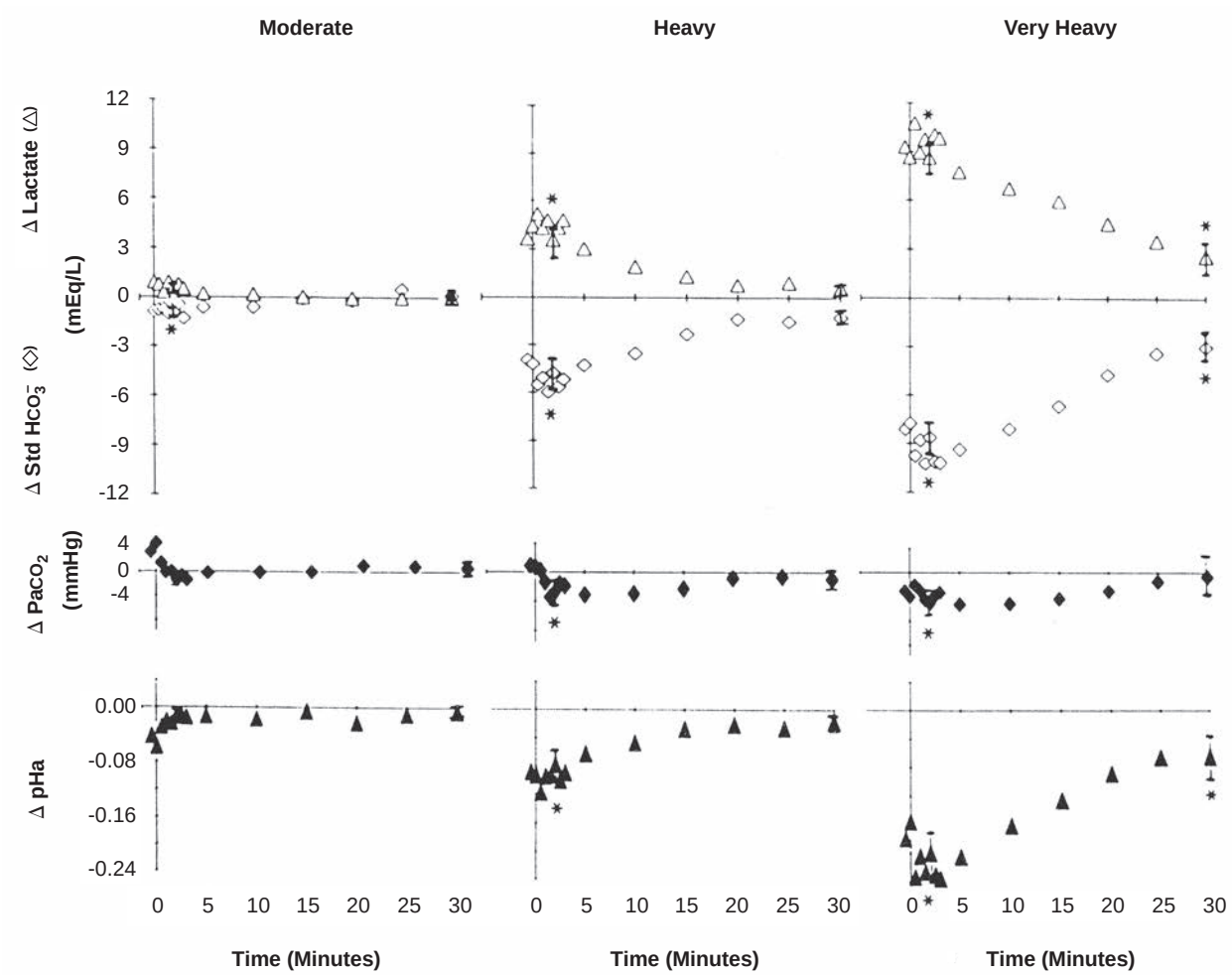

FIGURE 2.47. Changes in lactate, standard HCO_3^-, pHa, and Pa_{CO_2} relative to resting values during 30 minutes of recovery from 6 minutes of moderate, heavy, and very heavy intensity constant work rate exercise. Points are the average of eight subjects. Standard errors and significant differences (*$P < .05$ from resting value) are shown at 2 and 30 minutes. (From Stringer W, Casaburi R, Wasserman K. Acid-base regulation during exercise and recovery in man. *J Appl Physiol.* 1992;72:954–961, with permission.)

Table 2.4

Theoretical Gas Exchange and High-Energy Phosphate Yield from Carbohydrate and Free Fatty Acid Oxidation for a Standardized Exercise Bout Requiring an O_2 Uptake of 1 L/min

	RQ	$\dot{V}O_2$ (L/min)	$\dot{V}CO_2$ (L/min)	~P:O_2	~P:CO_2	O_2:~P	CO_2:~P
Carbohydrate (glucose)	1.0	1.0	1.0	6.00	6.00	0.17	0.17
Free fatty acid (palmitate)	0.7	1.0	0.7	5.65	8.13	0.18	0.12

RQ, respiratory quotient.

performed with fatty acids as the dominant substrate compared to carbohydrate, as predicted from the difference in ~P:O_2 ratios for the two substrates.

Heart Rate

Because heart rate increases linearly with $\dot{V}O_2$, the higher $\dot{V}O_2$ required for a given level of exercise when fatty acids are the substrate should predictably demand a higher cardiac output. This is reflected in a higher heart rate response when fatty acids are the dominant substrate as compared to carbohydrate (see Fig. 2.48, right panel).

Carbon Dioxide Production

While $\dot{V}O_2$ and heart rate are less at a given work rate when carbohydrate is the major substrate, $\dot{V}CO_2$ decreases when fat is the major source of energy.[19,127] This is predicted on the basis of the lower RQ for fat than for carbohydrate (see Table 2.4). However, the effect is more striking at rest than during exercise. Sue et al.[127] found that a low-carbohydrate diet affected resting much more than exercise $\dot{V}CO_2$, RQ, and $\dot{V}E$. Apparently, the muscles are able to extract carbohydrate from even a low-carbohydrate diet, making the muscle substrate RQ higher than most other organs in the body except for the brain. Thus, the muscles select the most oxygen-efficient fuel for aerobic work (see Fig. 2.3).

Ventilation

The steady-state ventilation is less for a given work rate with a predominant fat substrate, consistent with the hypothesis that the ventilatory control mechanisms are linked to CO_2 production. When $\dot{V}E$ is plotted as a function of $\dot{V}CO_2$, the relation is the same whether the RQ is high or low. Thus, a consistent relation is observed among normal subjects when $\dot{V}E$ is plotted against $\dot{V}CO_2$ (see Fig. 2.39). However, when $\dot{V}E$ is plotted against $\dot{V}O_2$,

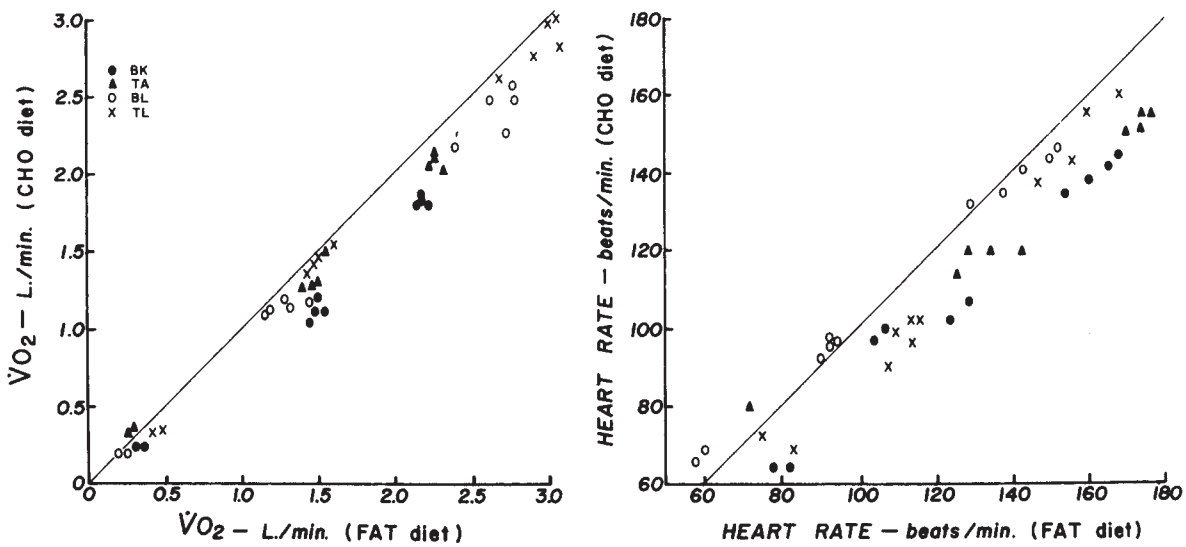

FIGURE 2.48. Effect of dietary substrate on oxygen consumption and heart rate during exercise. Studies were done on four subjects at rest and during two levels of exercise after 3 days on a high-carbohydrate diet (respiratory quotient [RQ] at rest = 0.97) and 3 days on a high-fat diet (RQ at rest = 0.75). The oxygen consumption is higher on the high-fat diet than on the high-carbohydrate diet during the performance of a given work rate. This is consistent with the biochemical evidence that the high-energy phosphate yield from fat is less than that from carbohydrate for a given O_2 cost. Heart rate during exercise is higher on the high-fat diet than on the high-carbohydrate diet, reflecting the link between oxygen consumption and cardiac output.

there is considerably more variability among subjects. This is due to RQ differences among subjects. When a high-RQ substrate is consumed, subjects have a steeper $\dot{V}_A$–$\dot{V}O_2$ slope than when a low-RQ substrate is consumed (see Fig. 2.45). The mechanism for the curvilinear steepening of $\dot{V}_E$ at the higher metabolic rates is accounted for by the ventilatory compensation for metabolic acidosis of heavy-intensity exercise shown in Figure 2.44.

CONTROL OF BREATHING

Despite a manifold increase in CO_2 production and O_2 utilization during exercise, as well as lactic acidosis at heavy-intensity exercise, the ventilatory control mechanisms systematically regulate arterial H^+ ($[H^+]a$), with small increase over the full range of constant and increasing metabolic rates in normal subjects (see Fig. 2.46)[4,105,125,148,152,160] and patients with various disorders.[123,128] Figure 2.46 shows the pattern of arterial hydrogen ion regulation over a wide range of time and work intensity.

Arterial Hydrogen Ion Regulation

Ventilation regulates $[H^+]a$ over the full range of exercise in normal subjects (see Figs 2.19, 2.23, 2.30, 2.41, and 2.46; see also specific cases in Chapter 10). The H^+ equivalents produced each minute in the form of CO_2 and lactic acid are extremely large as compared to H^+ content in the aqueous fluids of the body. Thus, to maintain $[H^+]a$ homeostasis, it is necessary to eliminate H^+, within seconds of production. This must be done by increasing ventilation in proportion to CO_2 and lactic acid production. The regulation of arterial H^+ accounts for the short duration of each breath during rest and the shorter and deeper breath during exercise.

H^+ Balance

H^+ in the Cellular Compartment

The average concentration of H^+ in the cell water is approximately 0.0001 mmol/L at pH of 7.0, the average pH of cell water at rest. Assuming 28 L of cell water (70-kg man), the total H^+ in the cell water compartment would be approximately 0.0028 mmol (0.0001 mmol/L × 28 L).

H^+ in the Extracellular Compartment

The average concentration of H^+ in the extracellular water is approximately 0.000044 mmol/L at pH of 7.36, which is the average pH of venous blood and therefore extracellular water at rest. Assuming a 14-L extracellular water compartment, the total H^+ in the extracellular water would be approximately 0.00062 mmol (0.000044 mmol/L × 14 L). Thus, the total H^+ in body water at rest is approximately 0.0028 + 0.00062 or 0.0034 mmol.

Arterial H^+ Regulation during Exercise without Lactic Acidosis

Exercise performed at a moderate work intensity (without a lactic acidosis) is, transiently, slightly hypercapnic (see Fig. 2.23; see also Chapter 3). The stress on the ventilatory controller to regulate arterial H^+ at approximately 40 nmol/L, the normal resting arterial H^+ concentration, is exemplified by the rate of H^+ produced when walking at 3.0 mph, without a lactic acidosis. This activity generates approximately 880 mL of CO_2/min or 40 mmol of respiratory H^+/min (application of Avogadro number – 880/22.3). This is about 11,800 times the H^+ in the total aqueous fluids of the body (40.0/0.0034).

Arterial H^+ Regulation during Exercise with a Lactic Acidosis

A metabolic acidosis due to increased blood lactate accumulation develops during heavy or higher exercise intensities, driving ventilation to induce hypocapnia (see Fig. 2.46). Assuming a work intensity that causes lactic acid to increase in the arterial blood at a rate of 0.5 mmol/min, and a lactate volume of distribution of 30% of body weight (21 L), the increase in total body H^+ from increased lactate production would be 15 mmol/min, or 4,400 times the content of H^+ in the aqueous fluids of the body. Because the buffering of the lactic acid is HCO_3^-, this additional H^+ equivalent over that produced by aerobic metabolism can also be eliminated from the body in the form of CO_2. During recovery (see Fig. 2.47), these reactions reverse, with the speed of recovery being only a few minutes for exercise at or below the *AT* to considerably longer for heavy and very heavy exercise intensities (above *AT*), depending on the rate of lactate catabolism.

The small changes in $[H^+]a$ actually observed during exercise attest to the remarkable ability of the ventilatory control mechanisms to regulate H^+ equivalents by initiating a breath every 4 seconds at rest and every 1.5 seconds with heavy exercise. Despite the nonuniformity of the H^+ increase in the body, the arterial chemoreceptors ventilate the pulmonary blood flow with remarkable precision, tracking H^+ production. Although tidal volume and breath duration vary in response to exercise, the net ventilatory response maintains near constancy of arterial H^+ during exercise, with a small H^+ error (see Fig. 2.46).

Patients with abnormal respiratory mechanics (e.g., chronic obstructive pulmonary disease or obesity) or impaired chemoreceptor function, or normal subjects breathing through an apparatus that imparts a high resistive load, can develop a significant respiratory acidosis due to CO_2 retention. However, respiratory alkalosis does not typically develop during exercise in normal subjects and is rarely seen in pathophysiological states.

In summary, Figures 2.23 and 2.46 show the acid–base changes in response to constant work rates of moderate, heavy, and very heavy intensity. The ventilatory response does not overshoot that needed to regulate pH. Characteristically, below the *AT*, the arterial pH is regulated at resting levels or slightly less because of a small increase in P_aCO_2.[155] For exercise above the *AT*, the acidosis becomes more marked due to a net increase in lactic acid production. This has a great effect on the ventilatory response to exercise because it increases the CO_2 produced in the buffering of lactic acid (22.3 mL of CO_2 for each mmol of HCO_3^- decrease). To constrain the fall in arterial pH caused by the elevation in lactate, a large ventilatory increase takes place (see Fig. 2.30 and Table 2.3). In recovery, as during exercise, pH homeostasis, rather than the level of P_aCO_2, seems to be the important metabolic determinant of ventilatory control (see Fig. 2.47).

Physical Factors

The physical factors that determine the alveolar ventilation were discussed earlier, in the section "Ventilatory Coupling to Metabolism". The current section is concerned with the physical factors that determine the actual ventilation ($\dot{V}_E$)—that is, the sum of the alveolar ventilation and the respired air that does not participate in normal gas exchange with the pulmonary circulation. $\dot{V}_E$ includes ventilation going to the anatomical dead space (conducting, non–alveoli-containing airways) and nonperfused or underperfused alveoli. This is the physiological dead space and is calculated as follows:

$$V_D = V_T\ (P_aCO_2 - P_ECO_2)/P_aCO_2$$

where P_ECO_2 is the CO_2 concentration in the mixed expired gas, V_T is the tidal volume, and V_D is the physiological dead space volume. Thus, the difference between the actual volume of air respired during breathing ($\dot{V}_E$) and the theoretical alveolar ventilation ($\dot{V}_A$) is dictated by V_D/V_T as follows:

$$\dot{V}_A = \dot{V}_E\ (1 - V_D/V_T)$$

To determine the $\dot{V}_E$ needed to eliminate a given quantity of CO_2, substitute $\dot{V}_E\ (1 - V_D/V_T)$ for $\dot{V}_A$ in the alveolar ventilation equation, shown in Figure 2.44, and solve for $\dot{V}_E$. The resulting equation is:

$$\dot{V}_E\ (BTPS) = 863\ \dot{V}CO_2\ (STPD)/P_aCO_2\ (1 - V_D/V_T)$$

where 863 is the product of the barometric pressure, temperature, and water vapor correction factors needed to express $\dot{V}_E$ as body temperature pressure saturated (BTPS), $\dot{V}CO_2$ as standard temperature pressure dry (STPD), and CO_2 as a partial pressure. From this equation, the quantity of breathing required for exercise is defined by three factors: the $\dot{V}CO_2$; the level or setpoint at which P_aCO_2 is regulated by the ventilatory control mechanisms; and the physiological dead space/tidal volume ratio. The influences of these three factors on $\dot{V}_E$ are graphically illustrated in Figure 2.44. (By substituting values in the equations shown in the figure, the axes in the figure can be scaled.) At work rates above the ventilatory compensation point for the exercise lactic acidosis (see Fig. 2.46), $\dot{V}_E$ and $\dot{V}_A$ increase nonlinearly, and steeply, with increasing $\dot{V}CO_2$ and decreasing P_aCO_2 (see Fig. 2.30).

Quadrant 1 of Figure 2.45 shows that the exercise $\dot{V}_E$ for a given O_2 cost of exercise (right-going horizontal axis) can be quite variable. The cause for this variability can be described by the physiological factors that contribute to $\dot{V}_E$. The first factor is the CO_2 produced as a result of the O_2 cost of work. This is defined by the equation $\dot{V}CO_2 = R \times \dot{V}O_2$ and plotted in quadrant 2. The R isopleths describe the ratio of CO_2 output resulting from aerobic metabolism and HCO_3^- buffering of lactic acid, relative to $\dot{V}O_2$. Quadrant 3 is derived from the alveolar ventilation equation, $\dot{V}CO_2 = \dot{V}_A \times P_aCO_2$, and takes into account variability in P_aCO_2. Finally, $\dot{V}_E$ is determined by adding the dead space ventilation to $\dot{V}_A$ as described in the equation for $\dot{V}_E$ given earlier (quadrant 4).

Reflexes Controlling Breathing during Exercise

Despite extensive research, there is no general agreement on the reflexes controlling ventilation during exercise. The observation that arterial pH, P_CO_2, and P_O_2 are essentially unchanged during moderate-intensity exercise has been difficult to explain, mechanistically, within the framework of the currently recognized stimuli and the manner by which they are thought to produce their reflex effects. The only chemoreceptors that have been clearly demonstrated to play an important role in the hyperpnea of exercise are the central chemoreceptors and the carotid bodies.[82] See the reviews by Whipp[160,161] and Wasserman, Whipp, and Casaburi[152] for a more detailed discussion of the mechanisms of the exercise hyperpnea. The following is a brief review of the reflex mechanisms proposed to play a role in the exercise hyperpnea.

Corticogenic or Conditioned Reflexes

The magnitude of the abrupt increase in $\dot{V}_E$ at the start of exercise (phase I) (Fig. 2.49) varies appreciably from individual to individual. However, high work rates generally result in only a slightly further increase in $\dot{V}_E$ at the start of exercise over that observed for the lightest loads. Consequently, for a low level work rate, the initial increase in phase I $\dot{V}_E$ is a larger fraction of the total ventilatory response than that for a heavy work rate (Figs. 2.49 and 2.50). The magnitude of the initial increase in $\dot{V}_E$ is

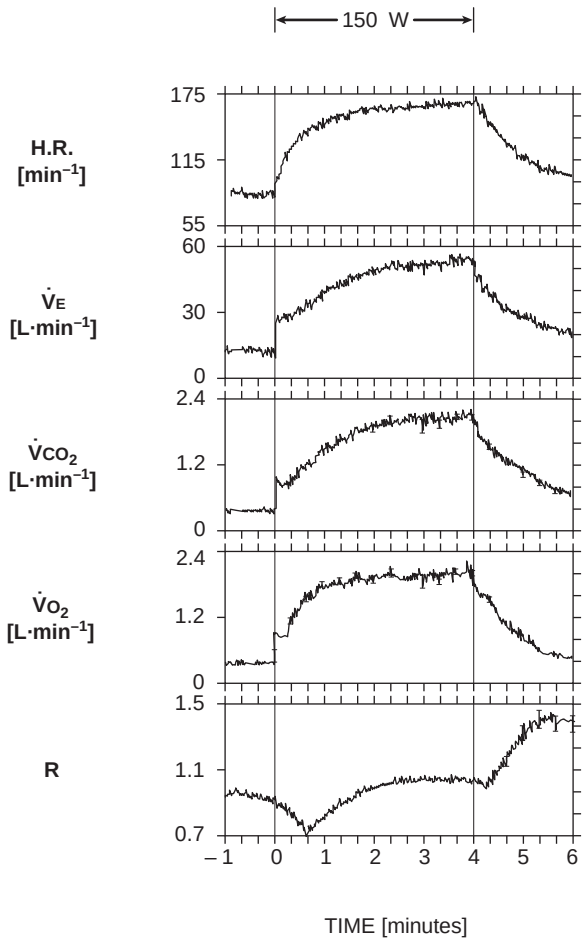

FIGURE 2.49. Changes in ventilation and gas exchange during cycle ergometer constant work rate exercise starting from rest (zero time) and ending at 4 minutes in a normal subject. This study is the average of six repetitions in which gas exchange was measured breath by breath and interpolated second by second. The *vertical bars* are the standard errors of the data. The abrupt increase in $\dot{V}_E$, $\dot{V}_{CO_2}$, and $\dot{V}_{O_2}$ at the start of exercise (zero time) is termed *phase I* and thought to be related, mechanistically, to the abrupt increase in pulmonary blood flow at the start of exercise. Respiratory exchange ratio (R) is usually unchanged from rest for about the first 15 seconds of exercise. The start of phase II is signaled by a decrease in R and is the period of exponential-like increase in $\dot{V}_E$, $\dot{V}_{CO_2}$, and $\dot{V}_{O_2}$ to their asymptotes (phase III). This is the period when increasing cellular respiration is reflected in lung gas exchange. R decreases transiently during phase II because $\dot{V}_{O_2}$ increases faster than $\dot{V}_{CO_2}$ due to gas solubility differences in tissues and phosphocreatine splitting (Fig. 2.26). It then increases to a value higher than rest because the respiratory quotient (RQ) of the exercising muscle substrate, being primarily glycogen, is higher than the average resting RQ.

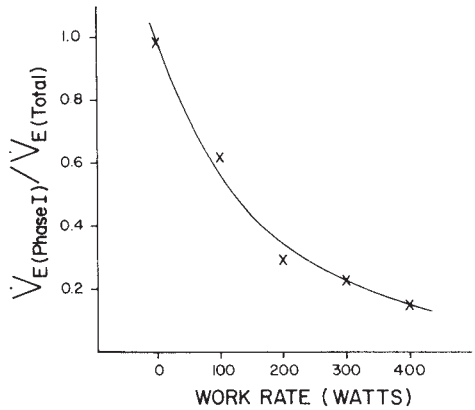

FIGURE 2.50. The magnitude of the phase I ventilatory response to exercise (from rest) as related to steady-state ventilation for various work rates. The higher the work rate, the smaller the fraction of the total ventilatory response attributable to phase I.

also not appreciably affected by different degrees of arterial oxygenation or functionality of the carotid bodies.[155]

Anxiety might account for part of the immediate ventilatory increase at the start of exercise (phase I) in some subjects. Krogh and Lindhard[80] suggested that the immediate $\dot{V}_E$ increase at the start of exercise might originate from the cerebral cortex as a conditioned reflex. Fink and associates[45] suggest that the cerebral cortex may play a role in the exercise hyperpnea beyond the initial ventilatory response. Martin and Mitchell[93] proposed that there may be a strong learning component to the ventilatory response—although this appears to be less prominent, if at all, in humans.[96] The studies of Eldridge et al.[42] and DiMarco et al.[39] in cats suggest that the initial ventilatory stimulus for the exercise hyperpnea might be mediated by the hypothalamus. Despite these important observations describing a neurogenic link to the initial and sustained ventilatory response to exercise, the patterns of ventilatory and gas exchange responses in humans suggest that the sustained ventilatory response is predominantly coupled to metabolism, and that the initial ventilatory (phase I) response might be linked to the circulatory response to exercise.[39,42,64,87,96,151,161,177] This linkage could account for the unchanging or very small change in pH, Pa_{CO_2}, and Pa_{O_2} and the ventilation and gas exchange transition between rest and exercise (see Figs. 2.49 and 2.50).

Respiratory Center and Central Chemoreceptors

The respiratory center includes collections of neurons in the brainstem that yield a rhythmic discharge to stimulate motor neurons to the respiratory muscles. Medullary lesions associated with tumors, primary hypoventilation syndromes, or central respiratory depression associated with hypoxia-inducing pulmonary diseases can cause the respiratory pacemaker mechanisms to depend on peripheral chemoreceptor input for providing a controlled rhythmic output. The apnea produced by O_2 administration in some patients with arterial hypoxemia is evidence that these pacemaker mechanisms may lose the required rhythmic discharge properties.

The central chemoreceptors do not appear to respond to the acute exercise-induced metabolic acidosis.[45,155] In

adult patients with primary alveolar hypoventilation syndrome (patients with normal pulmonary function but with hypercapnia and markedly diminished or absent ventilatory response to CO_2 breathing), the ventilatory response to exercise is diminished not only because they have rest and exercise hypercapnia (high CO_2 setpoint), but also because their arterial P_{CO_2} increases further with exercise.[86] However, it is difficult to know if this occurs secondary to central insensitivity to CO_2 or if it is due to a failure of the respiratory center to effectively integrate the afferent stimuli to give an appropriate ventilatory output. Furthermore, children with this syndrome have been reported to have normal ventilatory response to exercise despite absence of response to inhaled CO_2.[122]

Carotid Bodies

Much has been learned about the role of carotid bodies during muscular exercise from studies on selected, asymptomatic asthmatic patients who had both carotid bodies resected but whose baroreceptors were left intact.[149,167] The ventilatory response to exercise was studied in these subjects when they (1) were asymptomatic; (2) had normal, or near normal, respiratory function; and (3) had normal exercise tolerance. Their ventilatory responses to exercise were different from those of normal subjects in four ways:

1. The subjects without carotid bodies did not increase their ventilatory drive in response to hypoxia,[87] nor did they decrease their ventilatory drive, even transiently, in response to acute hyperoxia.[167] The available evidence is consistent with the carotid bodies being the only chemoreceptors in humans that induce hyperpnea in response to hypoxia.
2. The subjects without carotid bodies failed to develop ventilatory compensation for the exercise-induced metabolic acidosis[155] and consequently evidenced a greater arterial acidemia during high-intensity exercise.
3. The subjects without carotid bodies had a slow rate of increase in ventilation in response to constant-load exercise compared to that of normal subjects, resulting in a transient arterial hypercapnia.[155]
4. The subjects without carotid bodies had a prolonged breathholding time (about twofold) compared to that of normal subjects, while breathholding after a deep breath of normal room air at sea level. Consequently, the P_{ETO_2} was much lower and the P_{ETCO_2} was much higher at the subject's breakpoint for the subjects in whom the carotid bodies were resected.[36]

In normal subjects, the ventilatory response following the transition to high work intensity exercise, from a low work rate control, is slowed and the amplitude is reduced by O_2 breathing.[26] O_2 breathing in normal subjects also slowed the ventilatory response to a constant work rate challenge in the presence of a lactic acidosis.[98] The greater the baseline acidosis, the greater the attenuation of the ventilatory response. Studies on the acute effect of hyperoxia on $\dot{V}_E$ support the concept that the carotid bodies have an important role in the normal ventilatory response to exercise.[51] Although the exact mechanisms mediating this response remain to be elucidated, several potential stimuli of the carotid bodies include increases in P_{CO_2}, K^+, osmolarity, catecholamines, reduction in P_{O_2}, and increase in arterial H^+ concentration.

Whatever the precise role of these potential stimuli in the control of breathing during exercise, studies in which exercise ventilation is continuously measured during a switch of the inspired gas from air to 100% O_2 show that ventilation is reduced transiently by approximately 15% to 20% in normal subjects. However, patients who develop arterial hypoxemia during exercise have a much greater transient decrease in the exercise hyperpnea (see example in Chapter 4) compared to subjects who are not hypoxic. In summary, sufficient evidence is available from acute studies in patients with carotid body resection and normal subjects and patients breathing 100% O_2 to ascertain that the carotid bodies play an important role in regulating transient changes in arterial H^+ concentration and arterial O_2.[26,107,155]

Aortic Bodies

The aortic bodies seem to be unimportant as ventilatory chemoreceptors in humans, in contrast with their role in some other animal species (e.g., cats and dogs). Removal of the carotid bodies alone has been shown to eliminate the ventilatory response to hypoxia and the acute metabolic acidosis of exercise.[87,155]

Vagal Reflexes

The lungs are richly innervated by branches of the vagus nerve. Although investigators have postulated that the vagus nerve might contribute importantly to the exercise hyperpnea, studies on the ventilatory response to exercise in awake dogs by Phillipson et al.[101] showed that vagal blockade, induced by bilateral cooling of the cervical vagus nerves, did not change the overall ventilatory response to exercise, although the breathing pattern was altered. The authors concluded that the vagus nerves were not important in the overall ventilatory response to exercise in dogs at the exercise levels studied (up to 4 times resting $\dot{V}_{O_2}$).

Mechanoreceptors in the Extremities

To explain the exercise hyperpnea, it had been widely postulated that stimulation of position receptors or muscle spindles in the exercising muscle play a major role in the genesis of exercise hyperpnea.[37] The principal argument in favor of an appreciable role for the neural afferents or ergoreceptors or metaboreceptors from exercising muscles

stems from the observation of an immediate increase in $\dot{V}E$ at the start of exercise (phase I) (Fig. 2.49), in advance of the predicted (although not actual) arrival of the products of exercise metabolism to known chemoreceptors.

Neurophysiological studies have helped clarify the possible role of afferents from the exercising limb in mediating the exercise hyperpnea.[94] Studies in which the transmission of stimuli in large, myelinated fibers (e.g., transmitting proprioception) was interrupted demonstrate that these receptors play only a small role, if any.[68] Hornbein et al.,[59] Hodgson and Mathews,[58] and Waldrop et al.,[136] using different approaches to stimulate the muscle spindles, demonstrated no significant role for these organs in the exercise hyperpnea. Stimulation of the type III and IV muscle afferents (i.e., unmyelinated or small myelinated neurons) has been demonstrated to induce hyperpnea.[73] However, blocking their afferent transmission does not appreciably impair the exercise hyperpnea.[44] This is consistent with work that demonstrates that the coupling of $\dot{V}E$ to metabolic rate ($\dot{V}CO_2$) is not abnormal in human subjects with complete spinal cord transection who "exercise" by means of electrical stimulation of the leg muscles.[1,17] Ponikowski and colleagues[103] have postulated that stimulation of muscle ergoreceptors accounts for the increased ventilation observed in patients with heart failure. But even if ventilatory stimuli originating in the exercising muscles are active during exercise, respiration is not stimulated with enough intensity by these signals to override the mechanisms that regulate arterial pH in normal subjects or patients with heart failure.[156]

Cardiodynamic Hyperpnea

Cardiovascular reflexes linked to the ventilatory control mechanism or increased venous return at the start of exercise have been proposed as alternative explanations to that of ergoreceptors or mechanoreceptors in the extremities to account for the immediate increase in $\dot{V}E$ at the start of exercise.[61,64,152,153] The abrupt increase in venous return at the start of exercise could deliver increased quantities of blood to receptor sites downstream from the pulmonary capillaries (i.e., arterial chemoreceptors such as the carotid bodies). If $\dot{V}A$ did not keep pace with the increase in pulmonary blood flow, PCO_2 and $[H^+]$ would increase and PO_2 would decrease at the carotid bodies. These changes could provide humoral feedback stimuli to the respiratory control mechanism (e.g., via carotid chemoreceptor mediation) in less than the circulation time from muscles to arterial chemoreceptors. That this mechanism plays a role in the rapid, immediate (phase I) $\dot{V}E$ response to upright exercise is evidenced by the observation that the phase I increase in ventilation is attenuated if the same exercise is performed in the supine position.[157] In the supine position, relatively static, desaturated, CO_2-rich blood is not stored in dependent parts of the body, such as in the upright still position, and the stroke volume is already elevated at rest to the level found during exercise.[24,157]

GAS EXCHANGE KINETICS

The $\dot{V}E$, $\dot{V}O_2$, and $\dot{V}CO_2$ responses following the onset of constant work rate exercise from rest can be characterized by three time-related phases, as shown by the experimental data in Figure 2.49. The mechanisms of the gas exchange dynamics in response to exercise, as seen in Figure 2.49, are schematized in Figure 2.51.

Phase I is usually characterized by an immediate increase in gas exchange at the start of exercise. It lasts for about 15 seconds and is accounted for by the abrupt increase in pulmonary blood flow consequent to the increase in heart rate and stroke volume at the start of exercise. This is the period before blood from the exercising muscles, modified by cellular metabolism, has appeared in the lungs. Because the composition of this blood was determined under conditions of rest, R is characteristically the same as at rest during phase I (see Fig. 2.49).

Phase II for $\dot{V}O_2$ lasts from about 15 seconds after exercise onset to approximately the third minute or less of exercise. It reflects the period of major increase in cellular respiration. If the exercise is below the *AT*, a steady state in $\dot{V}O_2$ is achieved by 3 minutes for healthy subjects (see Fig. 1.4). If the exercise is above the *AT*, the steady state in $\dot{V}O_2$ is delayed or not achieved before the subject fatigues (see Figs. 1.4 and 2.6).

Phase III reflects the period of the steady-state $\dot{V}O_2$ if the work rate is below the *AT*. If the work rate is above the subject's *AT*, the rate of increase in $\dot{V}O_2$ during phase III correlates with the magnitude of the lactate increase (Fig. 2.52).[114,166,177]

Oxygen Uptake Kinetics

During the steady state, oxygen uptake from the lungs ($\dot{V}O_2$) reflects the oxygen consumed by the cells (see Fig. 2.6). During phase II of exercise, $\dot{V}O_2$ is equal to the O_2 consumed by the cells plus the creditors of the O_2 debt. These include the decrease in oxyhemoglobin in the venous blood, physically dissolved O_2, change in oxymyoglobin in the contracting muscles, decrease in muscle PCr, and anaerobic glycolysis (Fig. 2.53).

Except for breath-by-breath noise, changes in lung gas stores have relatively little effect on $\dot{V}O_2$ kinetics for two reasons: the concentrations of alveolar gases change very little and, in normal subjects, the net change in end-expiratory lung volume is usually no more than 0.5 L. Since 0.5 L of alveolar gas contain about 75 mL of O_2, a change in functional residual capacity (FRC) during phase I or II would have little impact on gas exchange kinetics. Despite these relatively small changes, an approach has been described to correct for both change in

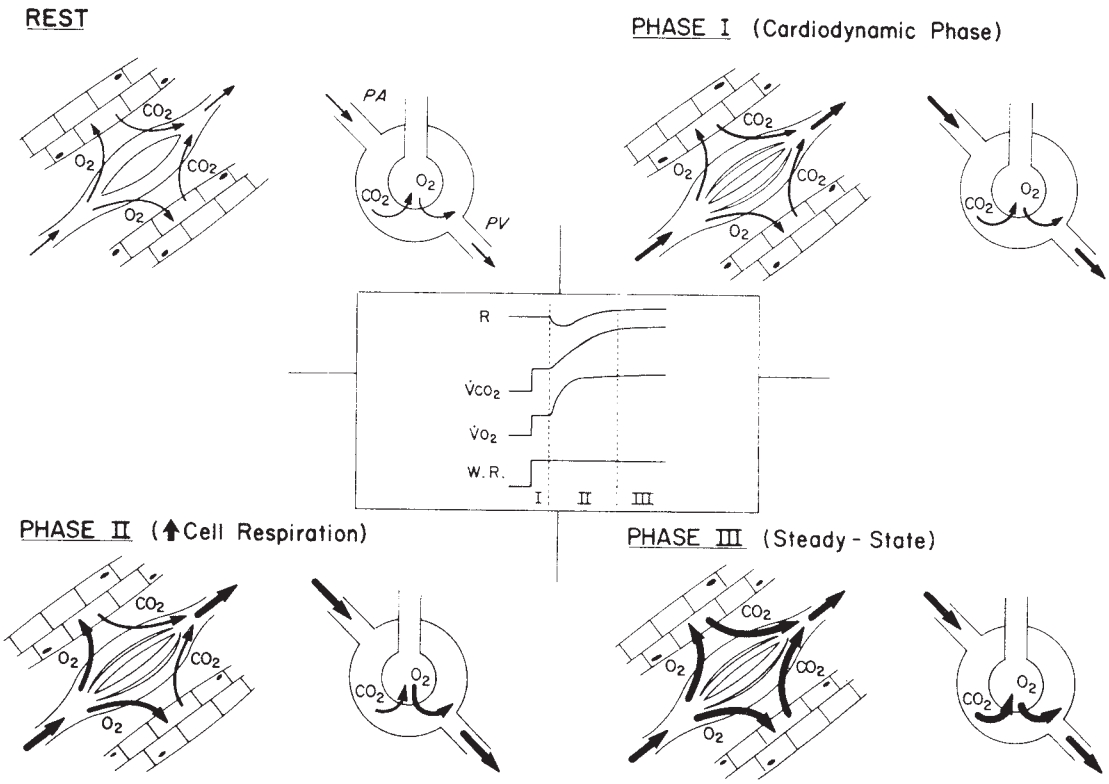

FIGURE 2.51. Gas exchange at the lungs in response to constant work rate exercise **(center diagram)**. Gas exchange at the cell **(left side of each quadrant)** couples to cardiorespiratory gas exchange **(right side of each quadrant)** through cardiovascular adjustments in the lungs and tissues. Phase I gas exchange is postulated to be caused by the immediate increase in cardiac output (pulmonary blood flow) at the start of exercise (cardiodynamic gas exchange). Phase II gas exchange reflects the decreased O_2 content and increased CO_2 content of the venous blood secondary to increased cell respiration as well as a further increase in cardiac output. (See *Sources of ATP Regeneration Reflected in $\dot{V}O_2$ and $\dot{V}CO_2$ Kinetics* in the text for an explanation of the decrease in R during phase II.) Eventually, a steady state is reached between internal and external respiration (phase III). PA, pulmonary artery; PV, pulmonary vein; WR, work rate. (From Wasserman K. Coupling of external to internal respiration. *Am Rev Respir Dis.* 1984;129(Suppl):S21–S24, with permission.)

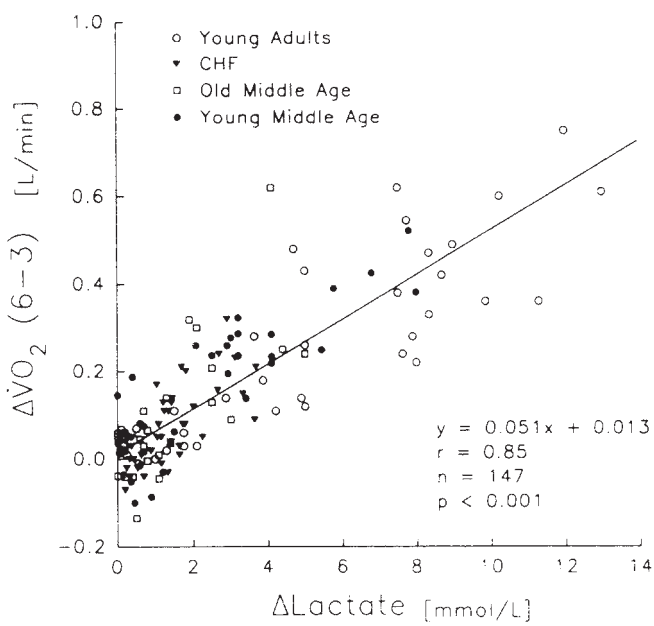

FIGURE 2.52. Increase in blood lactate (above resting value) as related to the difference in oxygen consumption between 3 and 6 minutes of constant work rate exercise in normal, young middle-aged, and late middle-aged adults and in patients with heart failure. Normally, $\dot{V}O_2$ does not increase after 3 minutes when the work is performed below or at the lactate threshold [$\dot{V}O_2$ (6 – 3) = 0]. CHF, cardiac heart failure. (Data from Roston WL, Whipp BJ, Davis JA, et al. Oxygen uptake kinetics and lactate concentration during exercise in humans. *Am Rev Respir Dis.* 1987;135:1080–1084; and Zhang YY, Wasserman K, Sietsema KE, et al. O_2 uptake kinetics in response to exercise: a measure of tissue anaerobiosis in heart failure. *Chest.* 1993;103:735–741, with the data on late middle-aged adults added.)

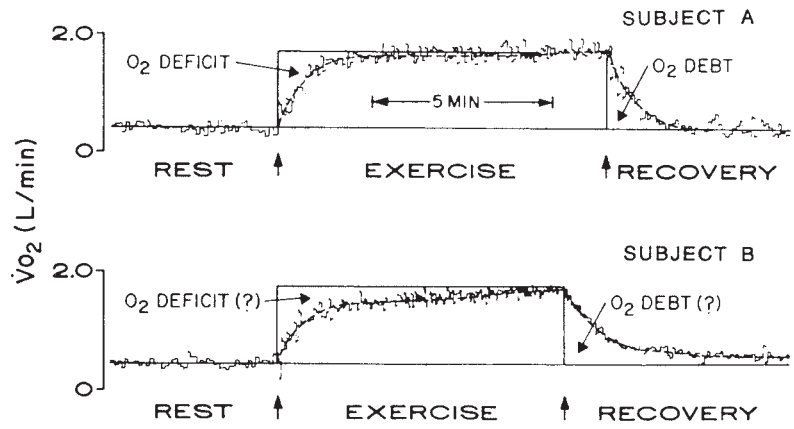

FIGURE 2.53. O_2 uptake kinetics in response to constant work rate exercise of 100 W in two subjects at different levels of fitness. This figure illustrates the effect of fitness on O_2 deficit and O_2 debt. See the text for precise definitions of O_2 deficit and O_2 debt.

alveolar concentration and change in lung volume for study of $\dot{V}O_2$ and $\dot{V}CO_2$ kinetics.[9]

The increase in $\dot{V}O_2$ may be quantified by the hemodynamic response to exercise [cardiac output and $C(a - \bar{v})O_2$]. At the onset of moderate exercise, oxygen uptake from the lungs approximately doubles the resting $\dot{V}O_2$ and then remains relatively unchanged during phase I. If $C(a - \bar{v})O_2$ did not increase during phase I, cardiac output could be inferred to have increased twofold. During upright exercise starting from the motionless sitting position, Casaburi et al.[25] showed that about one-third of the phase I $\dot{V}O_2$ may be accounted for by the abrupt increase in $C(a - \bar{v})O_2$ at the start of exercise. This is apparently due to blood stasis during rest in the upright resting condition. If stasis is prevented with elastic wraps on the legs, the abrupt increase in $C(a - \bar{v})O_2$ at the start of exercise disappears.[24] The phase I increase is greatly reduced when exercise is performed in the supine position[157] or following prior mild exercise.[164]

During phase II, $\dot{V}O_2$ increases as a single-exponential function with a time constant of approximately 30 to 45 seconds for a work rate below the *AT*.[18,23] If the exercise intensity is heavy or very heavy for a normal subject, or if the subject is so impaired that the cardiovascular response is inadequate to supply the total oxygen need, the increase in $\dot{V}O_2$ can be significantly slowed, and a steady state is not achieved by 3 minutes (see Figs. 1.4 and 2.38). In this metabolic state, lactate continues to increase until the $\dot{V}O_2$ reaches an asymptote.[144] A steady state in $\dot{V}O_2$ is achieved and can be sustained only when all of the cellular energy requirements are derived from reactions using oxygen transferred from the atmosphere.

Oxygen Deficit

The O_2 deficit is traditionally computed as the difference between the total oxygen uptake during an exercise bout and the product of the steady-state $\dot{V}O_2$ and the exercise duration (Fig. 2.53). A correct estimate of O_2 deficit can be obtained for exercise below the *AT* because the steady state is approached monoexponentially.[163] Above the *AT*, however, the complexity of judging the phase III asymptote—and even of assuming that there is a single exponential increase in $\dot{V}O_2$—makes a justifiable computation of the deficit tenuous.

Oxygen Debt

The oxygen debt is the difference between the total oxygen uptake in excess of the resting oxygen uptake, or other appropriate control level, during the recovery period (see Fig. 2.53).[56] Once $\dot{V}O_2$ reaches a steady state during exercise at or below the *AT*, the oxygen debt no longer increases, regardless of the exercise duration.[120] In this instance, the O_2 debt will be repaid within 5 minutes of recovery. If the work is above the *AT*, the O_2 debt can be quite high and may not be repaid for an hour or more. The size of the O_2 debt is linked to the increase in blood lactate concentration.[92] As long as the oxygen uptake does not reach a steady state and lactate continues to rise during constant work rate exercise, the O_2 deficit and debt will continue to increase. For work levels at which a true steady state in $\dot{V}O_2$ can be achieved (i.e., at or below the *AT*), the size of the O_2 debt approximates that of the O_2 deficit.[163]

Mean Response Time

The averages of replicate second-by-second measurements of $\dot{V}O_2$, $\dot{V}CO_2$, and R for four different levels of constant work rate exercise are shown in Figure 2.54 for a normal subject. The data are the second-by-second average of four replicate studies. For the 25-W exercise level, it is evident that about 80% of the $\dot{V}O_2$ required to perform the work (steady-state $\dot{V}O_2$) was achieved during phase I (within 15 seconds of the start of exercise), the cardiodynamic phase of gas exchange. The fraction of the phase I contribution to the steady-state $\dot{V}O_2$ decreases at higher work rates, so that phase II kinetics become more important in achieving the O_2 requirement.

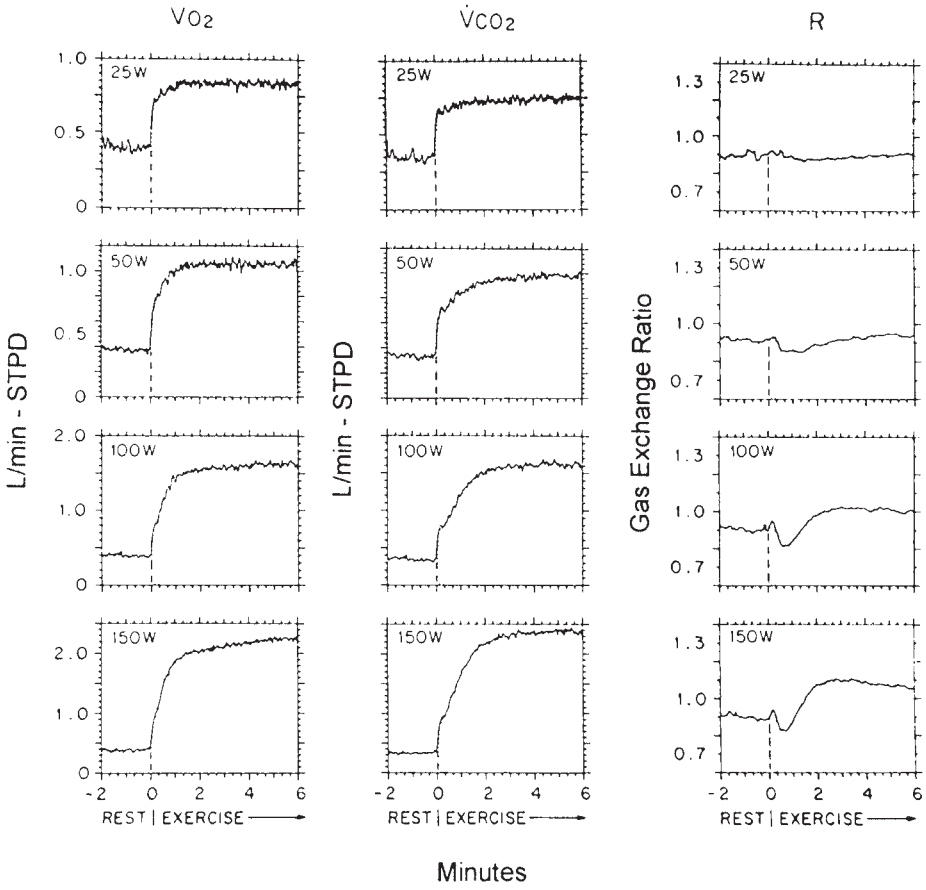

FIGURE 2.54. $\dot{V}O_2$, $\dot{V}CO_2$, and the respiratory gas exchange ratio (R) at four cycle ergometer work rates, starting from rest and cycling for 6 minutes at the work rates indicated, for a normal male subject. The *vertical dashed line* indicates the time of start of exercise. Each work rate was repeated four times on different days, and the breath-by-breath data were interpolated second by second. These values were then time-aligned to zero and time-averaged each second to reduce random noise and enhance the reproducible responses. (Data taken from study reported in Sietsema K, Daly JA, Wasserman K. Early dynamics of O_2 uptake and heart rate as affected by exercise work rate. *J Appl Physiol.* 1989;67:2535–2541.)

The subject studied in Figure 2.54 is below his *AT* at 50 W, with $\dot{V}O_2$ being in steady state by 3 minutes. However, the subject is clearly above his *AT* at 150 W since $\dot{V}O_2$ continues to increase and $\dot{V}CO_2$ increases above $\dot{V}O_2$. Because the $\dot{V}O_2$ kinetics are informative with respect to determining fitness and the presence of disease in the gas transfer function, there has been considerable interest in its quantification. Because the actual data do not conform to a single-exponential relation, the mean response time (MRT) has been used for quantification of the kinetics of the $\dot{V}O_2$ response. The MRT characterizes the combination of the phase I and II $\dot{V}O_2$ dynamics and is obtained by performing a single-exponential fit through the overall response, treated as if it were monoexponential from exercise onset. The time constant of the response so treated (i.e., 63% of the asymptotic exponential fit) is defined as the MRT (Fig. 2.55). The additional useful feature of the MRT, as so determined, is that when multiplied by the steady-state $\dot{V}O_2$ response amplitude, it yields the best-fit determination of the oxygen deficit.

The $\dot{V}O_2$ MRTs of 10 different subjects at five different work rates are related to fitness (maximum $\dot{V}O_2$ per kg) in Figure 2.56. This figure shows that MRT is similar among subjects of differing fitness at very low work rates (e.g., unloaded or zero watts cycling) because even unfit normal individuals can achieve a steady-state $\dot{V}O_2$ response during phase I of very light work. However, as work rate is increased, the discrimination in fitness becomes more obvious. The subjects with the highest $\dot{V}O_2$max have the lowest MRT for a given work rate.

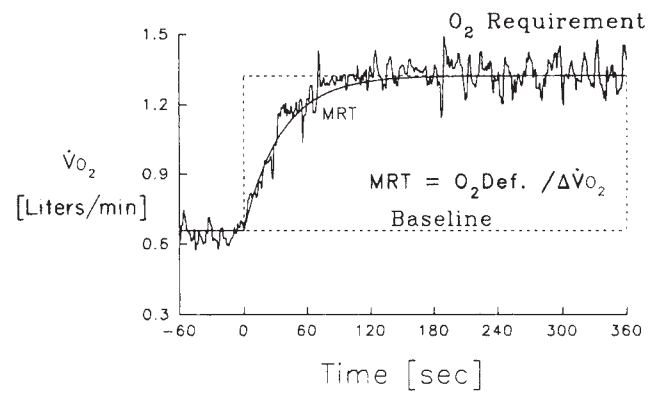

FIGURE 2.55. Illustration of method for calculating $\dot{V}O_2$ mean response time (MRT) for constant work rate exercise from breath-by-breath data. A single exponential best-fit curve is put through the data, and the time constant (63% of the asymptotic response) for the increase in $\dot{V}O_2$ above baseline is calculated. If there were no O_2 deficit, the $\dot{V}O_2$ would reach a steady state during the first breath, and the MRT would be 0. As shown in the equation, the O_2 deficit can be calculated from the MRT and the steady-state increase in $\dot{V}O_2$ above baseline.

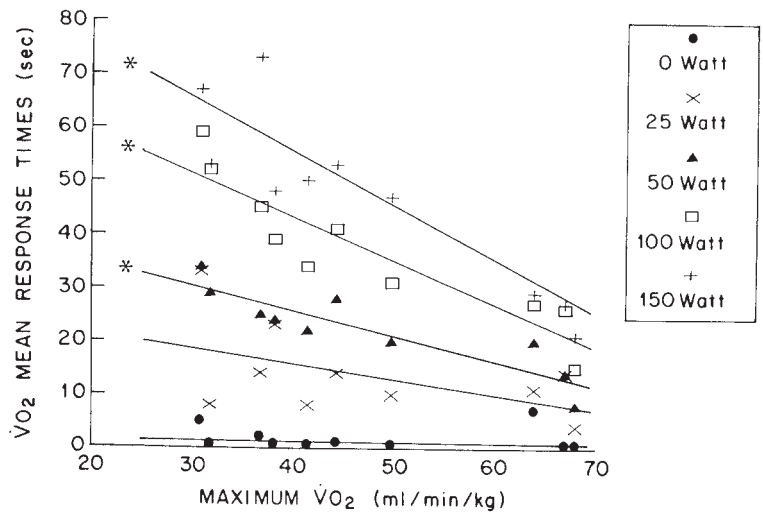

FIGURE 2.56. Mean response times (MRT) in 10 normal subjects, at the work rates indicated, as related to the subject's maximum $\dot{V}O_2$ (mL/min/kg). At work rates of 50 W and higher, the MRT becomes greater as the subject becomes less fit. (From Sietsema K, Daly JA, Wasserman K. Early dynamics of O_2 uptake and heart rate as affected by exercise work rate. *J Appl Physiol.* 1989;67:2535–2541, with permission.)

In summary, if phase I is a large fraction of the steady-state response for a given work rate, the MRT, O_2 deficit, and debt will be small (see Fig. 2.56). In contrast, if phase I is small, the O_2 deficit and debt will be relatively large. The O_2 deficit and debt will also be large if the phase II $\dot{V}O_2$ kinetics for a given work rate are slow (e.g., the 150-W work rate in Figs. 2.54 and 2.56). Because $\dot{V}O_2$ kinetics are faster for the more fit subject (see Fig. 2.56), he or she will have a smaller O_2 deficit and debt for a given work rate.

Carbon Dioxide Output Kinetics

For below-*AT* exercise, $\dot{V}CO_2$ has slower kinetics than $\dot{V}O_2$ (steady state may not occur until 4 minutes or more). The time of maximum reduction in R is usually at about 30 to 45 seconds (see Figs. 2.49 and 2.54). The period of the decrease in R identifies when CO_2 produced aerobically is not being entirely eliminated by the lungs, but is being stored in the tissues.[30] The relatively slow kinetics for $\dot{V}CO_2$ might be explained by the following reactions:

1. The hydrolysis of PCr fixes CO_2 as HCO_3^-.
2. As venous oxyhemoglobin saturation decreases, the reduced hemoglobin is capable of holding more CO_2 at the same PCO_2 (Haldane effect).
3. The increase in muscle PCO_2 puts more CO_2 in physical solution at the same pH.

Because hydrolysis of PCr contributes to the ~P consumption at the beginning of exercise and this reaction produces an alkalinizing reaction,[102,115] CO_2 produced in the muscle from aerobic metabolism is retained as HCO_3^-. Thus, $\dot{V}CO_2$ increases more slowly than $\dot{V}O_2$, and R decreases at approximately 15 to 45 seconds after the start of constant work rate exercise before it increases (see Figs. 2.49 and 2.54).[30] The increase in R to a constant value (after the decrease) reflects the substrate RQ in the contracting muscle groups. If a lactic acidosis occurs during the exercise, $\dot{V}CO_2$ increases faster than $\dot{V}O_2$ due to the additional CO_2 formed as HCO_3^- dissociates during the buffering reaction (see Fig. 2.37). This generally starts after about 40 seconds of constant work rate exercise (see Fig. 2.36). Thus, R will overshoot the steady-state R, as seen at 150 W for the subject illustrated in Figure 2.54 until lactate stops increasing.

SUMMARY

The major physiological responses to exercise are summarized in Figure 1.3. Approximately 28% of the calories generated during work are transformed into useful external work, while the remaining 72% are lost primarily as heat. The oxidative energy obtained from oxygen creditors (hemoglobin, myoglobin, creatine ~*P*, and pyruvate conversion to lactate) during the O_2 deficit period, which must be repaid during the recovery period of exercise as the O_2 debt, varies with the work rate. If the subject is very fit for the work rate, the O_2 deficit and debt are relatively small. At moderate work rates, the pyruvate-to-lactate mechanism provides none or a very small fraction of the creditors of the O_2 deficit. In contrast, for very heavy work rates, the pyruvate-to-lactate mechanism may account for upward of 80% of the total O_2 deficit.[148]

Gas exchange during exercise should be considered from the standpoint of cellular respiration and how cardiovascular and ventilatory mechanisms are coupled to it. Not only does the magnitude of cellular respiration affect external respiration, but, importantly, the degree to which the work rate is above the subject's *AT* has a major influence on the cardiovascular and ventilatory responses to exercise. The *AT* is reduced when the cardiovascular transport of O_2 is impaired. Exercise above the *AT* increases CO_2 and H^+ production, with both having powerful effects as ventilatory stimuli. The gas exchange kinetics are also altered and exercise endurance is reduced above the *AT*.

The peripheral blood flow distribution depends on the work rate and local humoral factors that optimize the

O_2 (blood) flow–metabolic rate relationship. Normally, heart rate is linearly correlated with oxygen consumption. Presumably because of local control mechanisms, the O_2 consumption to muscle blood flow ratio and thereby the end-capillary P_{O_2} in the exercising muscles are relatively uniform. The relative uniformity of the regional O_2 uptake/blood flow relationship enables the muscle end-capillary P_{O_2} to be sufficiently high in all muscle capillary beds to allow as much as 85%, on average, of the O_2 to be extracted from the muscle blood flow during maximal exercise.

During exercise, minute ventilation responds to the changing rate of CO_2 delivered to the lungs, including that generated by aerobic oxidation of energy substrate and that generated by the buffering of lactic acid by HCO_3^-. In addition, the carotid bodies monitor arterial H^+ ($[H^+]a$), providing sufficient ventilatory drive to minimize the increase in $[H^+]a$. Exercise ventilation is also determined by the size of the physiological dead space ventilation and the level at which arterial P_{CO_2} is regulated. Arterial P_{O_2} remains relatively constant during exercise, despite increasing $\dot{V}O_2$.

Incremental exercise tests that measure $\dot{V}O_2$ and $\dot{V}CO_2$ breath by breath allow detection of the *AT* by gas exchange. Also, breath-by-breath measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ during constant work rate exercise can be used to determine if the exercise is being performed with or without a lactic acidosis and to estimate the magnitude of the lactate increase at the work rate performed.

$\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ abruptly increase at the start of exercise (phase I), particularly when the exercise is performed in the upright position. After the first 15 seconds of constant-load exercise, $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ rise exponentially (phase II) to a steady state or an asymptote (phase III). Their kinetics are influenced by cellular metabolism and fitness factors. During phases II and III, $\dot{V}E$ closely follows the changing rate of CO_2 delivery to the lungs rather than the actual CO_2 produced or the O_2 consumed, if the exercise is performed without a lactic acidosis. $\dot{V}E$ increases disproportionately to $\dot{V}O_2$ when the exercise is performed above the anaerobic (lactic acidosis) threshold, with a subsequent disproportionate, and acid–base regulatory, increase relative to $\dot{V}CO_2$. Breath-by-breath gas exchange measurements in response to appropriately chosen work rate protocols can therefore provide considerable insight into mechanisms of cardiovascular and ventilatory control and the state of cellular respiration.

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CHAPTER

3

Changes in Blood Gases and pH during Exercise

The energy requirement of exercise is supported by the blood transport of oxygen, carbon dioxide, and H^+ ion; the amount of aerobically and anaerobically produced energy dramatically affects the values of these variables in blood. The changes in arterial, venous, and muscle capillary blood gas composition reflect the efficiency of lung gas exchange, cardiovascular function, peripheral blood flow distribution, muscle capillarization, and muscle metabolism. This chapter describes the changes in oxygen and carbon dioxide content in arterial, mixed venous, and muscle venous blood; the effects of H^+ ion concentration on these values; the likely mechanisms responsible for these changes; the balance of H^+ ion production and excretion during exercise; and the relationship of cardiac output to oxygen uptake during exercise in normal subjects.

OXYGEN, CARBON DIOXIDE, AND H^+ ION TRANSPORT

P_{O_2}

During progressively increasing work (ramp-pattern) cycle ergometer exercise, arterial P_{O_2} at sea level remains high (>80 mm Hg) and relatively constant throughout exercise (Fig. 3.1A), while mixed venous and femoral vein blood P_{O_2} values fall very rapidly to approximately 20 mm Hg, reflecting the increased extraction of O_2 in support of muscle metabolism. The mixed venous and femoral vein P_{O_2} values are virtually superimposed from the anaerobic threshold (~54% $\dot{V}O_2$max) to end exercise.

Oxygen Content

Blood oxygen content (see Fig. 3.1B) is calculated from hemoglobin concentration ([Hb]), oxygen saturation (S_{O_2}), and arterial P_{O_2}, as shown in the following equation[16]:

$$O_2 \text{ content (mL } O_2\text{/100 mL)} = [\text{Hb}] \text{ (g/dL)} \times S_{O_2} \times 1.34 \text{ mL } O_2\text{/g Hb} + (0.003 \times P_{O_2})$$

The oxygen content of blood as a function of P_{O_2} (mm Hg) has a sigmoid relationship (Fig. 3.2), with a plateau value in arterial blood of approximately 20 mL per 100 mL in normal adults (using a value of 15 g/dL of hemoglobin). The P_{50}, or the P_{O_2} at which the hemoglobin is 50% saturated, is approximately 28 mm Hg at pH of 7.40, P_{CO_2} of 40, and temperature of 37° C. The remarkable characteristic of blood is the increase in oxygen content, above that physically dissolved (only 0.3 mL per 100 mL at a P_{O_2} of 100 mm Hg), related to the strong oxygen-binding properties of the hemoglobin molecule. Arterial oxygen content for a given P_{O_2} increases as a function of exercise intensity above the lactic acidosis threshold (*LAT*) (see Fig. 3.1B). The values and mechanisms are discussed in Chapter 2.

Mixed venous and femoral vein oxygen content decreases progressively during exercise. However, the decrease in mixed venous oxygen content above the *LAT* is primarily due to increasing blood acidification (see Fig. 3.1E, F) since the P_{O_2} values are virtually unchanged (see Fig. 3.1A). Arteriovenous oxygen content differences [$C(\bar{v} - a)O_2$] are maximally increased during peak exercise due to the combination of a progressive fall in the mixed venous values and an increase in the arterial oxygen content (see Fig. 3.1B).

Several mechanisms assist oxygen content loading in the pulmonary circulation and unloading in the peripheral circulation,[16] including hemoglobin.

- *Hemoglobin:* In the lung, hemoglobin exhibits increased O_2 affinity as more oxygen molecules are bound to each successive hemoglobin subunits as the blood CO_2 and H^+ are simultaneously reduced. Also, blood undergoes a small hemoconcentration above the *LAT* (see Fig. 3.1B) due to a shift of extracellular fluid into cells. The mechanism is described in greater detail in Chapter 2. In the tissues, oxygen has a decreased affinity for hemoglobin as oxygen molecules are unbound in the muscle capillary bed because of the decreasing muscle P_{O_2} (steep part of the oxyhemoglobin dissociation curve) and increasing blood CO_2 and H^+ (*Bohr effect*).

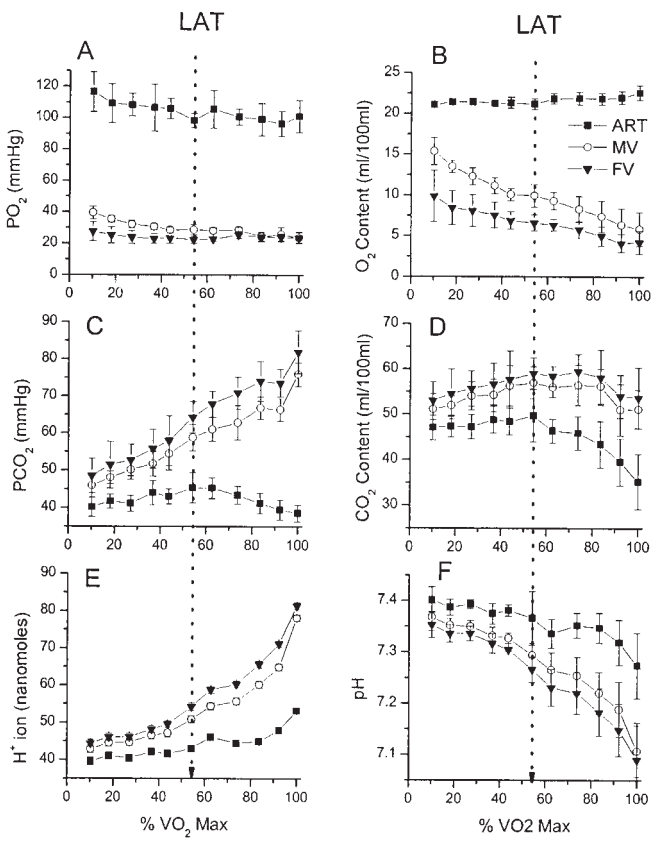

FIGURE 3.1. P_{O_2} **(A)**, O_2 content **(B)**, P_{CO_2} **(C)**, CO_2 content **(D)**, H^+ ion concentration **(E)**, and pH **(F)** as a function of exercise intensity (%$\dot{V}o_2$max) (mean ± standard deviation) in arterial (■, ART), mixed venous (○, MV), and femoral vein (▼, FV) blood during ramp pattern increasing work rate exercise (n = 5). Lactic acidosis threshold (*LAT*) (54% of $\dot{V}o_2$max) is shown by the vertical dashed line. The results are the average of five normal male subjects. (From Stringer W, Hansen J, Wasserman K. Cardiac output estimated non-invasively from oxygen uptake ($\dot{V}o_2$) during exercise. *J Appl Physiol.* 1997;82:908–912, with permission.)

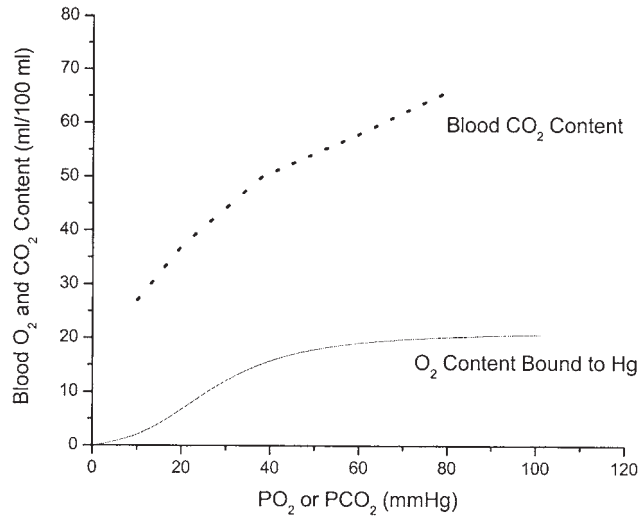

FIGURE 3.2. Blood carbon dioxide content, oxygen content, and dissolved oxygen in milliliters per 100 mL as a function of partial pressure of O_2 and CO_2 (pH = 7.4, T = 37° C, P_{50} = 28 mm Hg, hemoglobin = 15 g/100 mL). Dissolved oxygen content is 0.3 mL/100 mL at 100 mm Hg P_{O_2}. The increase in arterial oxygen content as a function of P_{O_2} is primarily related to oxygen bound to hemoglobin. Blood CO_2 content as a function of increase in P_{CO_2} is quite steep in the physiologic range. (CO_2 content data are from Christiansen J, Douglas CG, Haldane JS. The dissociation of CO_2 by human blood. *J Appl Physiol.* 1913;47:ii.)

- *Bohr effect:* O_2 affinity for hemoglobin increases in the pulmonary capillary blood as H^+ and P_{CO_2} are decreased in the lung. O_2 affinity for hemoglobin decreases in the peripheral capillary blood as muscle H^+ and P_{CO_2} increase.
- *Temperature:* Decreasing temperature shifts the oxyhemoglobin dissociation curve to the left, increasing affinity of hemoglobin for O_2, whereas increasing temperature, such as in an active muscle generating heat, shifts the curve to the right, thereby facilitating O_2 dissociation from hemoglobin.
- *2,3-diphosphoglycerate:* Increasing 2,3-diphosphoglycerate concentrations shift the curve to the right, whereas decreasing concentrations shift the curve to the left (this effect is small compared with H^+ ion effect).

A leftward shift of the oxyhemoglobin dissociation curve in the pulmonary capillary bed, where P_{CO_2} decreases and pH increases, assists oxygen loading. A rightward shift enhances oxygen unloading in the muscle during exercise, where increased P_{CO_2}, reduced pH, and increased temperature are present. Therefore, the characteristics of the oxygen content curve with respect to P_{O_2} are not static. They are subject to constant change depending on the local environmental and metabolic factors throughout the round trip from central to peripheral circulations.[22]

P_{CO_2}

Arterial P_{CO_2} increases slightly on average during moderate leg-cycling exercise up to the *LAT*, and then decreases below the resting value by the end of exercise (see Fig. 3.1C). Mixed venous and femoral vein P_{CO_2} values increase progressively during exercise, with the highest values occurring in the femoral vein. CO_2 content is high relative to arterial oxygen content—approximately 48 mL per 100 mL at an arterial P_{CO_2} of 40 mm Hg—compared with an arterial O_2 content of 20 mL per 100 mL at a P_{O_2} of 100 mm Hg (Fig. 3.2). Arterial CO_2 content (see Fig. 3.1D) remains essentially constant around 46 mL per 100 mL up to the *LAT* metabolic rate. Above that, it decreases dramatically (to 35 mL per 100 mL) due to the marked fall in arterial pH and arterial P_{CO_2}. Mixed venous and femoral vein CO_2 content are elevated relative to arterial values and progressively increase until the *LAT*, above which progressive buffering of the lactic acidosis by bicarbonate (HCO_3^-) decreases CO_2 content. The maximal increase in venous–arterial CO_2 content difference $[C(\bar{v} - a)CO_2]$ is due to a more rapid fall in arterial CO_2 content rather than to an increase in mixed venous CO_2 content for exercise above the *LAT*.

H^+ Ion

The total H^+ ion concentration in cells (pH ~7.00) is 0.0001 mmol/L. In a 70-kg man, 28 L of cell water would contain 0.0028 mmol. In the 14-L extracellular water compartment (pH ~7.36), the total H^+ is approximately 0.00063 mmol. Thus, total H^+ in body water is ~ 0.0028 + 0.00063, or 0.0034 mmol. This is a relatively small amount of H^+ ion, considering the large rate of H^+ produced per minute in the form of CO_2 during normal walking speed of about 3 mph, or 30 mmol per minute. Thus, the H^+ produced during walking exercise each minute is approximately 10,000 times that present in the aqueous body fluids (40 nmol vs. 3.4×10^{-3} mmol), reflecting the great precision with which H^+ must be regulated during exercise (calculated H^+ turnover rate of 10,000 per minute; i.e., $40/(3.6 \times 10^{-3})$ mmol per minute). H^+ quantification, and its regulation by ventilation, is further discussed in Chapter 2.

Arterial H^+ concentration as a function of exercise intensity (see Fig. 3.1E) is only slightly increased up to the *LAT*. Above the *LAT* work rate, it begins to increase much more rapidly. Mixed venous and femoral vein H^+ are higher than arterial H^+ during all phases of exercise, increasing more rapidly above the *LAT* to the highest levels at end of exercise. In addition, the values for the mixed venous and femoral vein H^+ are similar throughout exercise, with the femoral vein H^+ being slightly higher. Arterial pH (see Fig. 3.1F) decreases slightly up to the *LAT*, and then more rapidly above the *LAT*. Mixed venous and femoral vein pH progressively decrease throughout exercise.

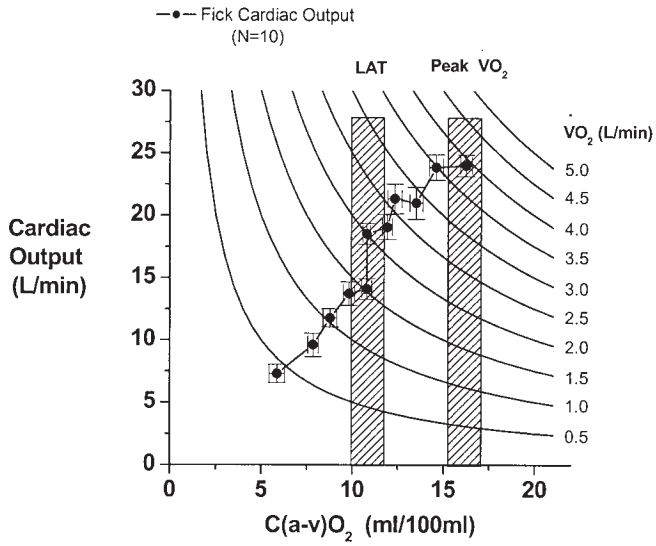

FIGURE 3.3. Fick cardiac output (CO) as a function of arterial–mixed venous oxygen content difference $[C(a - \bar{v})O_2]$ (mean ± standard error of mean) during exercise for 10 studies in five young normal men with mean resting hemoglobin of 15 g per 100 mL. $\dot{V}O_2$ isopleths, as well as the average lactic acidosis threshold (*LAT*) and peak $\dot{V}O_2$ values (*hashed bars*), are shown. Cardiac output increases on average from 7.5 L/min (unloaded cycling) to approximately 25 L/min at end of exercise, with a value of approximately 15 to 17 L/min at the *LAT*. $C(a - \bar{v})O_2$ increases on average from 5 mL per 100 mL at rest to 16 mL per 100 mL at peak exercise. $\dot{V}O_2$ increases from below 0.5 L/min for unloaded cycling to 2 L/min at the *LAT*, to nearly 4 L/min at peak exercise. Peak $\dot{V}O_2$ is dependent upon maximal increases in Fick cardiac output and $C(a - \bar{v})O_2$ content difference. (From Stringer W, Hansen J, Wasserman K. Cardiac output estimated non-invasively from oxygen uptake ($\dot{V}O_2$) during exercise. *J Appl Physiol.* 1997;82:908–912, with permission.)

THE RELATIONSHIP BETWEEN CARDIAC OUTPUT AND OXYGEN UPTAKE DURING EXERCISE

Oxygen uptake ($\dot{V}O_2$) during exercise (Fig. 3.3) is related to the product of cardiac output and arterial–mixed venous oxygen content difference $[C(a - \bar{v})O_2]$:

$$\dot{V}O_2 = \text{Cardiac output} \times C(a - \bar{v})O_2$$

The highest $\dot{V}O_2$ isopleth, or highest aerobic production of ATP, is obtained by simultaneously, and maximally, increasing the cardiac output and the arterial–mixed venous oxygen content difference (see Fig. 3.3).

Cardiac output has been well studied during exercise[4,12,20,21,25–27,29,32] and is a function of heart rate (HR) and stroke volume (SV): Cardiac output = HR × SV. Figure 3.4 typifies the changes in cardiac output that are found in healthy young adult male subjects. Cardiac

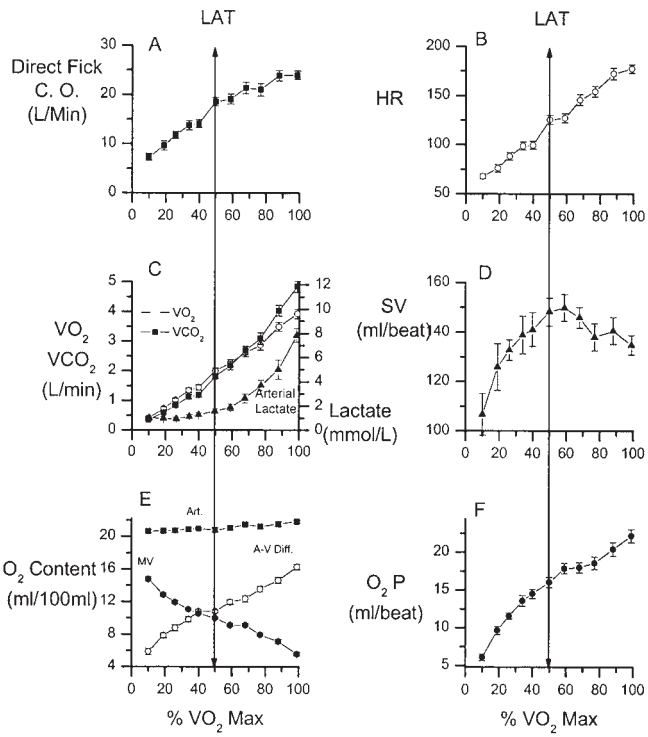

FIGURE 3.4. Measurement (mean ± standard error of mean of 10 studies in five subjects) during a ramp protocol cycle ergometer exercise test for the same subjects shown in Figure 3.3. Cardiac output (CO, L/min) **(A)**; heart rate (HR, beats/min) **(B)**; oxygen uptake ($\dot{V}O_2$, L/min), carbon dioxide output ($\dot{V}CO_2$, L/min), and arterial lactate (mmol/L) **(C)**; stroke volume (mL/beat) **(D)**; arterial and mixed venous oxygen contents and a–v oxygen content differences (mL/100 mL) **(E)**; and O_2 pulse (mL O_2/beat) **(F)** in the same subjects as Figure 3.3, as a function of percent $\dot{V}O_2$ max during ramp pattern progressive work rate exercise (mean ± standard error of mean). Vertical arrows at 50% $\dot{V}O_2$ max mark the mean lactic acidosis threshold (*LAT*). (From Stringer W, Hansen J, Wasserman K. Cardiac output estimated noninvasively from oxygen uptake ($\dot{V}O_2$) during exercise. *J Appl Physiol.* 1997;82:908–912, with permission.)

output progressively increases during exercise (see Fig. 3.4A). The HR response is essentially linear as a function of percent $\dot{V}O_2$ max from 70 to 180 beats per minute (see Fig. 3.4B). $\dot{V}O_2$, $\dot{V}CO_2$, and lactate as a function of work intensity all increase dramatically during a ramp-pattern work rate forcing, with $\dot{V}CO_2$ exceeding $\dot{V}O_2$ when the anaerobic threshold is exceeded due to HCO_3^- buffering of lactic acid (see Fig. 3.4C). SV increased from 100 mL per beat at rest to 150 mL per beat at the *LAT*. Above the *LAT*, SV decreased slightly on average to approximately 135 mL per beat at end of exercise (see Fig. 3.4D). Thus, cardiac output increased from the *LAT* to peak exercise due to HR increase. The arterial, mixed venous oxygen contents, and $C(a-\bar{v})O_2$ are displayed as functions of percent of $\dot{V}O_2$ max and exercise intensity in Figure 3.4E. Oxygen pulse, or the amount of oxygen extracted from each heartbeat, increased progressively, but more slowly from the *LAT* to peak exercise (see Fig. 3.4F).

The arterial–venous oxygen content difference during exercise is maximized by a small arterial content increase as mixed venous O_2 content decreases with increasing exercise intensity (see Fig. 3.4E). Several studies[21,31,32] have shown that arterial oxygen content increases approximately 5% to 8% due to an approximate 1.0 to 1.5 g/dL hemoglobin increase secondary to hemoconcentration above the *LAT*, as described in Chapter 2. Therefore, the oxygen-carrying capacity in the arterial blood normally increases from approximately 20.5 mL per 100 mL at the start of exercise to 21.5 mL per 100 mL (~5%) at the end of exercise (see Fig. 3.4E).[31] At the *LAT* (~50% of $\dot{V}O_2$ max), the mixed venous blood is approximately 50% to 60% desaturated in normal subjects (oxygen content of 9–10 mL per 100 mL; see Fig. 3.4E). At the end of exercise (peak $\dot{V}O_2$), the mixed venous oxygen content had decreased to approximately 5 mL per 100 mL, or one-third of the initial mixed venous oxygen content.

Muscle O_2 extraction during leg cycling exercise has been studied in normal subjects by examining arterial–femoral vein O_2 partial pressures and content differences during incremental and constant work rate exercise. The objective was to better understand the effects of muscle

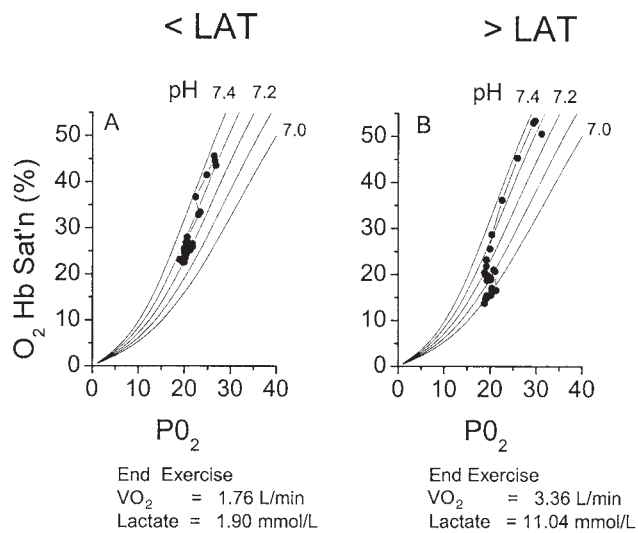

FIGURE 3.5. Femoral vein oxyhemoglobin saturation (*O_2Hb Sat'n*) as a function of Po_2 during 6 minutes of constant work rate exercise below (<*LAT*) **(A)** and above (>*LAT*) **(B)** the anaerobic threshold (n = 5). pH isopleths for the lower portion of the oxyhemoglobin dissociation curve are superimposed upon the experimental data. The end exercise lactate concentrations and $\dot{V}O_2$ for both exercise bouts are shown beneath the graphs. (From Stringer W, Wasserman K, Casaburi R, et al. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J Appl Physiol.* 1994;76:1462–1467, with permission.)

metabolism and tissue production of acid (metabolic production of CO_2 and lactic acid) on femoral vein blood gases and S_{O_2}.[1,24,29,32] During moderate constant work rate exercise below the *LAT*, the fall in pH is initially related to the increase in metabolic production of CO_2 (Fig. 3.5). Femoral vein S_{O_2} falls from 45% to 28% with a modest decrease in pH (7.35–7.30; Fig. 3.5B). However, with constant work rate exercise intensity above the *LAT*, there are two components to this fall in oxyhemoglobin saturation: the early component due to the fall in femoral vein P_{O_2} with a relatively small decrease in pH, and then a decrease in oxyhemoglobin saturation without a further fall in femoral vein P_{O_2} (see Fig. 3.5B). The latter takes place due to the critical capillary P_{O_2} having been reached, with increased production of H^+ with lactate as the metabolic demand increases. The increased H^+ (decrease in pH) enables O_2 to dissociate from hemoglobin without a decrease in P_{O_2} (Bohr effect).[3]

Estimating Cardiac Output

The progressive increase in oxygen uptake during exercise is achieved by a combination of increases in both cardiac output and arterial–venous oxygen content differences. The linear relationship of $C(a-\bar{v})O_2$ as a function of percent $\dot{V}O_2$ max (Fig. 3.6) allows cardiac output to be estimated with respect to percent $\dot{V}O_2$ max,[31] modifying the $C(a-\bar{v})O_2$ value for [Hb] and percent arterial O_2 saturation. These values compare favorably with directly measured cardiac output using the Fick principle

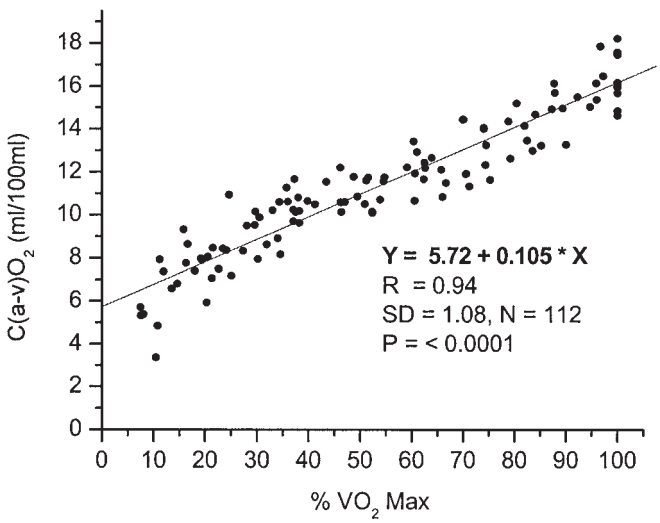

FIGURE 3.6. Arterial–mixed venous oxygen content difference [$C(a-\bar{v})O_2$] as a function of percent $\dot{V}O_2$ max during ramp exercise for 10 studies on five normal young men. $C(a-\bar{v})O_2$ is linearly correlated with percent $\dot{V}O_2$ max: $C(a-\bar{v})O_2 = 5.72 + (0.105 \times \%\ \dot{V}O_2max)$. (From Stringer W, Hansen J, Wasserman K. Cardiac output estimated noninvasively from oxygen uptake ($\dot{V}O_2$) during exercise. *J Appl Physiol.* 1997;82:908–912, with permission.)

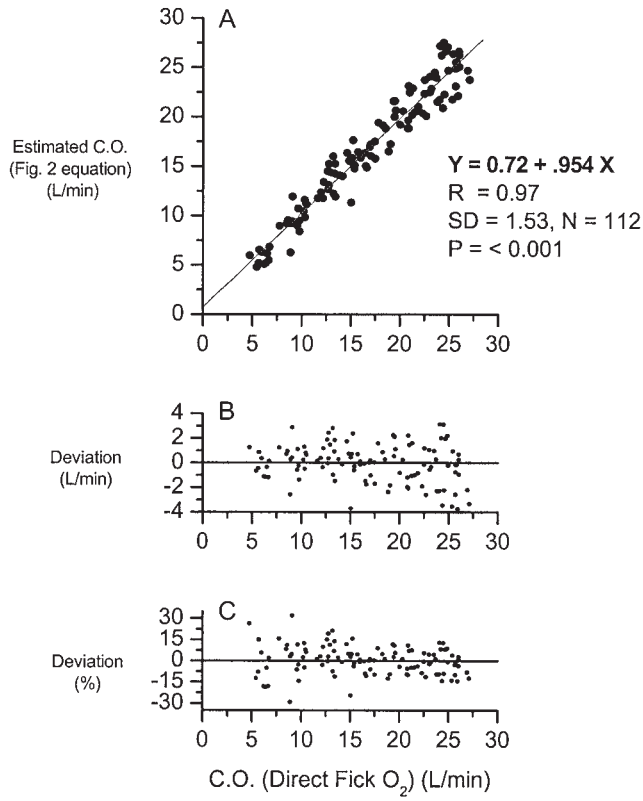

FIGURE 3.7. Estimated cardiac output (CO) from measured $\dot{V}O_2$ and estimated $C(a-\bar{v})O_2$ (determined from the equation in Figure 3.6) compared with directly measured Fick CO during progressive ramp exercise **(A)**. The estimated and measured values agree well **(B)**, with a 95% confidence limit of ± 15% **(C)**. (From Stringer W, Hansen J, Wasserman K. Cardiac output estimated non-invasively from oxygen uptake ($\dot{V}O_2$) during exercise. *J Appl Physiol.* 1997;82:908–912, with permission.)

(Fig. 3.7). Cardiac output by the Fick principle[15] can also be calculated from the measured CO_2 output ($\dot{V}CO_2$) and $C(a-\bar{v})CO_2$ content differences during exercise.[34] The increased variability of Fick principle–derived CO_2 cardiac output compared with O_2 cardiac output is attributable to the much lower extraction ratio for CO_2 and the greater complexity in calculation of blood CO_2 as compared with O_2 contents. Because of the large variability of results related to estimating cardiac output from direct measurements of $\dot{V}CO_2$ and arterial and mixed venous CO_2 contents, these results raise substantial concerns about the accuracy and precision of estimating cardiac output using CO_2 as the test gas, even in normal subjects.[2,7–11,14,17–19]

CARBON DIOXIDE TRANSPORT

Although CO_2 can bind to hemoglobin and other proteins to create reversible carbamino groups ($RNH_2 + CO_2 \leftrightarrow RNHCOOH \leftrightarrow RNHCOO^- + H^+$),[23] a specific transport

protein is not required since CO_2 is more soluble than O_2 in blood and converts, when hydrated, to form a relatively strong acid (carbonic acid, pKi = 3.8)[5,6,23]:

$$\underset{\text{CA}}{\overset{\text{Kh}}{\leftrightarrow}}\ H_2CO_3 \underset{3.8}{\overset{\text{Ki(1)}}{\leftrightarrow}}\ HCO_3^- + H^+ \underset{>10}{\overset{K_2}{\leftrightarrow}}\ CO_2^{2-} + 2H^+$$

Carbonic anhydrase (CA) in the red blood cells catalyzes the hydration of CO_2 to H_2CO_3. The molecular weight of carbonic anhydrase is approximately 30 K, and three isoforms are observed. The red blood cell has two types: I (low activity) and II (high activity). A third type (III) is observed in slow-twitch muscle fibers. The active site of all three types contains a zinc ion; acetazolamide, a drug that inhibits CA enzyme activity, binds to zinc.[23] CA is found in red blood cells and the pulmonary endothelium, as well as other sites in the body (e.g., kidney, choroid plexus). The log form yields the more familiar equation (Henderson–Hasselbalch equation):

$$pH = pKa' + \log([HCO_3^-]/[s \times P_{CO_2}])$$

where s = 0.0307 mM/Torr at 37° C in human plasma, and pKa′ is 6.10 (the apparent dissociation constant, when the hydration and ionization reactions [Kh and Ki] are combined).

The vast majority of CO_2 (88%) is carried as HCO_3^- in arterial blood, with physically dissolved and carbamino CO_2 accounting for 5% and 7% of the CO_2 transported, respectively. CO_2 reacts with carbamino groups at two sites: the α-terminal NH_2 group (one per protein chain), and ε-lysine residues in contact with fluid (many per protein chain). About 40% of total carbamino is formed at epsilon sites at pH of 7.40 and P_{CO_2} of 40; the remainder is formed on alpha sites.

Although a well-defined titrimetric method for evolution and measurement of the total CO_2 has been developed to assess CO_2 content,[28,30] it is rarely used today in clinical medicine. Therefore, we calculate blood CO_2 content based on an equation that uses pH, P_{CO_2}, and hemoglobin[13]:

$$\text{Blood } C_{CO_2} = \text{Plasma } C_{CO_2} \times \left[1 - \frac{(0.0289 \times [\text{Hb}])}{(3.352 - 0.456 \times S_{O_2}) \times (8.142 - \text{pH})}\right]$$

and

$$\text{Plasma } C_{CO_2} = 2.226 \times s \times \text{Plasma } P_{CO_2} \times [1 + 10^{(\text{pH} - \text{pKa}')}]$$

where [Hb] is hemoglobin concentration in g/dL, 2.226 is the conversion factor for mM/L to mL/100 mL, and s and pKa′ are as defined previously. When oxygen dissociates from hemoglobin, the deoxygenated hemoglobin absorbs H^+ ion:

$$Hb\ (O_2)_4 + 2.4\ H^+ \leftrightarrow Hb\ (H) + 4\ O_2$$

Therefore, the decrease in H^+ manifests as an increase in pH, which increases CO_2 content via increased HCO_3^-.

CO_2 transport during exercise is a very interesting demonstration of the changes in CO_2 content in the various blood compartments as a result of pH and P_{CO_2} perturbations (Fig. 3.8). From rest to the *LAT*, the arterial P_{CO_2} increases slightly, from a mean of 40 mm Hg to a maximum of 43 mm Hg (see Fig. 3.8A). As exercise progresses, there is a fall in Pa_{CO_2} to a value below the resting value (37 mm Hg) at end of exercise. Simultaneous values in the mixed venous blood increase in a linear fashion as a function of exercise intensity, from a resting mean value of 47 mm Hg to approximately 80 mm Hg at peak exercise (see Fig. 3.8A). CO_2 content in the arterial blood follows a similar contour to the arterial P_{CO_2}. However, the decrease in arterial CO_2 content at end of exercise is greater than the decrease in arterial P_{CO_2} because of the significant fall in arterial pH during exercise (see Fig. 3.8B). Resting arterial CO_2 content is 21 mM (or 21 × 2.226 = 46.7 mL per 100 mL, where 2.226 is the conversion factor for mM/L to mL per 100 mL), and resting mixed venous CO_2 content is 23 mM (or 51.1 mL per 100 mL), both of which are more than twice the corresponding resting arterial oxygen contents (9.5 mM or 21.1 mL per 100 mL; see Fig. 3.8D).

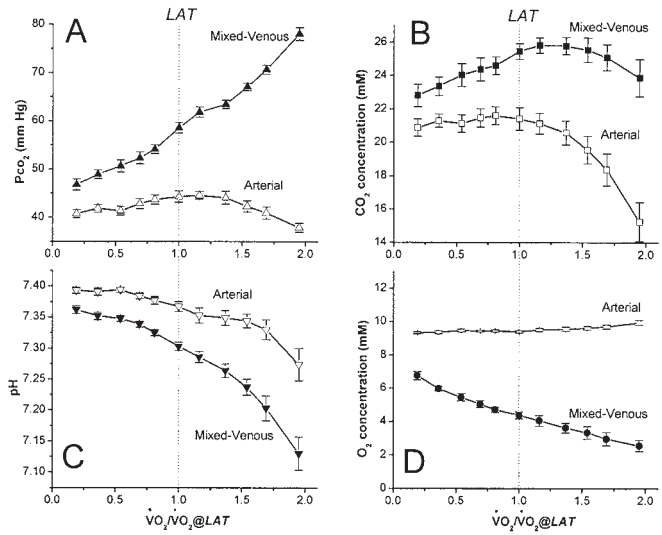

FIGURE 3.8. Arterial and mixed venous P_{CO_2} **(A)**, CO_2 concentration **(B)**, pH **(C)**, and O_2 concentration **(D)** (mean ± standard error of mean) as a function of exercise intensity, below (<1.0) and above (>1.0) the lactic acidosis threshold (*LAT*), where $\dot{V}O_2$ /($\dot{V}O_2$ at *LAT*) = 1.0. (From Sun XG, Hansen JE, Stringer WW, et al. Carbon dioxide pressure-concentration relationship in arterial and mixed venous blood during exercise. *J Appl Physiol.* 2001;90:1798–1810, with permission.)

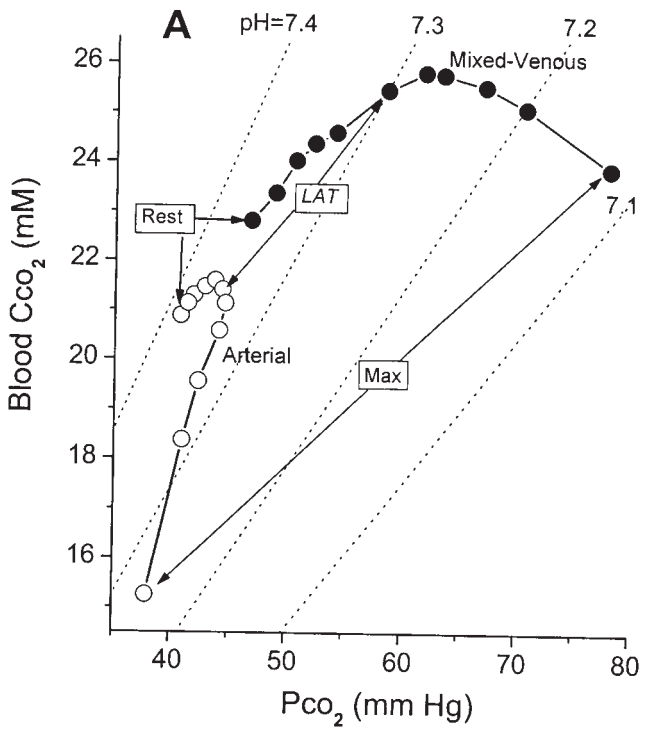

FIGURE 3.9. Arterial and mixed venous blood CO_2 concentration during incremental ramp exercise as related to P_{CO_2} and pH. Above the lactic acidosis threshold (*LAT*), despite the continuing increase in P_{vCO_2}, the major mechanism accounting for increasing $C(\bar{v} - a)CO_2$ was the decrease in P_{aCO_2} and C_{aCO_2}. (From Sun XG, Hansen JE, Stringer WW, et al. Carbon dioxide pressure-concentration relationship in arterial and mixed venous blood during exercise. *J Appl Physiol.* 2001;90:1798–1810, with permission.)

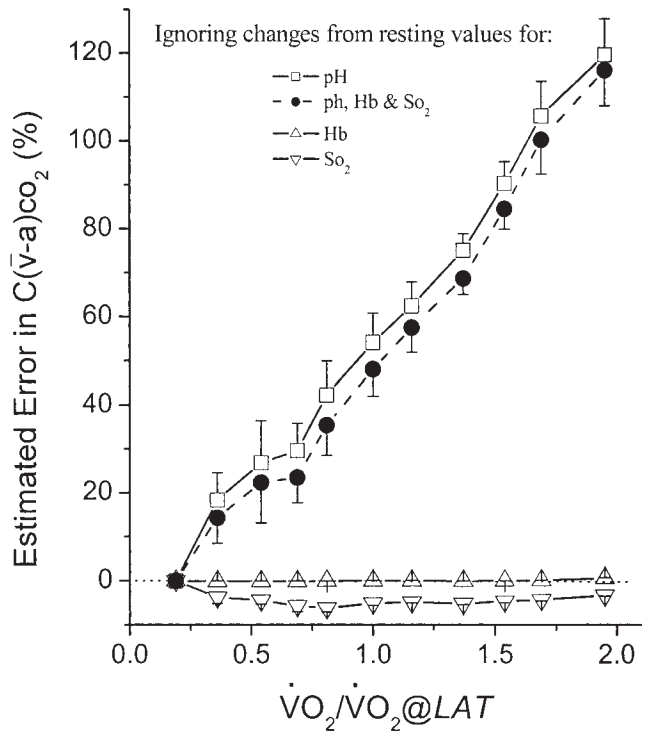

FIGURE 3.10. Relative contributions for the estimated error caused by ignoring changes from rest to exercise of pH, hemoglobin (Hb), oxyhemoglobin saturation (S_{O_2}), and the three combined to the $C(\bar{v} - a)CO_2$ during exercise. The *x*-axis units are the same as Figure 3.8. Clearly, pH has the dominant effect on carbon dioxide content. (From Sun XG, Hansen JE, Stringer WW, et al. Carbon dioxide pressure-concentration relationship in arterial and mixed venous blood during exercise. *J Appl Physiol.* 2001;90:1798–1810, with permission.)

The CO_2 content in the mixed venous blood initially increases to maximum values just above the *LAT*. However, as exercise intensity increases further, the CO_2 content falls in the mixed venous blood (despite increasing P_{CO_2}) to a value very similar to the resting mixed venous CO_2 content. This directional change in CO_2 content as compared with P_{CO_2} in mixed venous blood is due to the overriding effect of the fall in pH (see Fig. 3.8C). Therefore, the increase in $C(\bar{v} - a)CO_2$ during heavy exercise is primarily due to the decrease in arterial CO_2 content relative to the mixed venous CO_2 content, not due to the increase in mixed venous CO_2 content. This differs from the mechanism of increasing $C(a - \bar{v})O_2$, which is primarily due to the decrease in mixed venous O_2 content and only a small increase in arterial O_2 content.

To better understand the changes in arterial and mixed venous blood CO_2 content with respect to changes in pH, the CO_2 content values have been graphed as a function of P_{CO_2} with pH isopleths (Fig. 3.9). Blood CO_2 content at rest in the arterial blood is approximately 21 mM; in the mixed venous blood, it is approximately 23 mM. Both increase slightly during early exercise due

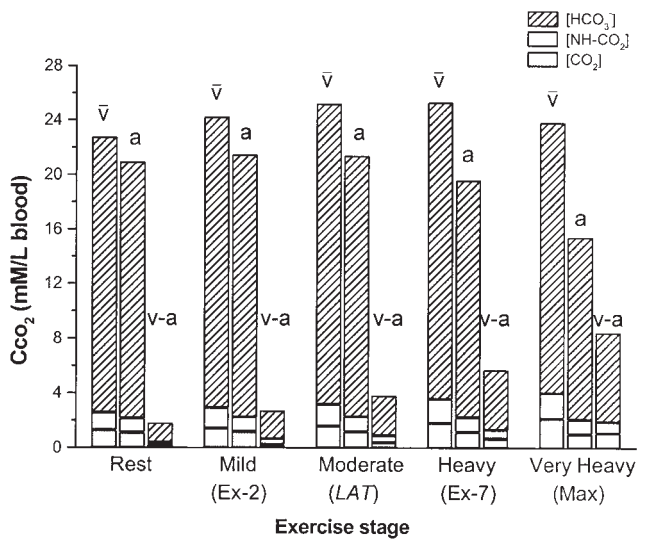

FIGURE 3.11. Blood CO_2 content (HCO_3^-, carbamino, and free CO_2) in the mixed venous ($\bar{v}$), arterial (a), and venous–arterial (v – a) difference as a function of exercise intensity (rest, mild, moderate, heavy, and very heavy exercise). (From Sun XG, Hansen JE, Stringer WW, et al. Carbon dioxide pressure-concentration relationship in arterial and mixed venous blood during exercise. *J Appl Physiol.* 2001;90:1798–1810, with permission.)

to the increase in P_{CO_2}. As the *LAT* is reached, arterial blood CO_2 content progressively falls to very low values, and the mixed venous value returns very close to its resting value. The marked fall in pH is related primarily to lactic acidosis that develops above the *LAT*. Thus, the increase in $C(\bar{v} - a)_{CO_2}$ difference at work levels below the *LAT* is primarily due to an increase in mixed venous blood CO_2 content, with little change in arterial values. In contrast, as exercise proceeds above the *LAT*, the arterial blood CO_2 content is progressively driven downward, primarily accounting for the increase in $C(\bar{v} - a)_{CO_2}$ difference at maximal exercise.

The effects of changes in pH, [Hb], and S_{O_2} on CO_2 content have been compared during exercise.[33] The changes in CO_2 content during exercise are essentially fully explained by the changes related to pH (Fig. 3.10), since the changes related to [Hb] and S_{O_2} are very small. The changes in relative proportions of forms of CO_2 carriage (HCO_3^-, carbamino, and free CO_2) during exercise are shown in Figure 3.11. HCO_3^- is the dominant form in which CO_2 is transported and accounts for the major increase in $C(\bar{v} - a)_{CO_2}$ at peak exercise.

SUMMARY

Mechanisms of oxygen and carbon dioxide transport are important physiological concepts that assist our understanding of the physiology of exercise. Oxygen transport optimization must occur during exercise to maximize aerobic energy production because anaerobic sources cannot sustain exercise. To achieve maximum O_2 transport, arterial oxygenation, [Hb], cardiac performance, and blood flow distribution must be functioning optimally. Cardiac performance can be evaluated using the Fick principle (using measured oxygen uptake during exercise and the recognized pattern of change for $C[a - \bar{v}]_{O_2}$). O_2 transport takes place in tandem with CO_2 transport rather than independently. Both are affected by the pH change accompanying lactate accumulation. Thus, while oxyhemoglobin dissociates more readily when H^+ is formed with lactate, HCO_3^- decreases due to it serving as the buffer of the H^+. Consequently, venous HCO_3^- and P_{CO_2} do not change in the same direction above the *LAT*. Optimal exercise performance depends on the effects of pH on oxygen and carbon dioxide transport.

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CHAPTER

4

Measurements during Integrative Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (abbreviated CPET or CPX) permits simultaneous evaluation of the ability of the cardiovascular and respiratory systems to perform their major function, that is, gas exchange between the cells and the environment.[2,58] Exercise requires an integrative cardiopulmonary response to support the increase in muscle respiration required for exercise. Therefore, gas exchange measurements are fundamental to the understanding of the pathophysiology of exercise limitation. It is evident from the scheme shown in Figure 1.3 that a reduction in $\dot{V}O_2$max (peak $\dot{V}O_2$) can be caused by any disease process affecting skeletal muscle function or the organ systems needed to transport O_2 and CO_2 between the air and the muscle cell. Use of CPET to determine only $\dot{V}O_2$max or peak $\dot{V}O_2$, as is commonly done, fails to employ this laboratory test to its fullest capacity, to define the pathophysiology of exercise limitation. This chapter describes measurements obtained from CPET that are useful when assessing the responses of each of the organ systems that couple external respiration (O_2 uptake and CO_2 output at the airway) to cellular respiration (O_2 consumption and CO_2 production of the cells) during exercise.

WHAT IS AN INTEGRATIVE CARDIOPULMONARY EXERCISE TEST?

The primary function of the cardiovascular and pulmonary systems is to support cellular respiration. The success of these organ systems in meeting this function is reflected in the O_2 uptake and CO_2 output in response to a specific work rate and their relation to heart rate, ventilation, and to one another. An integrative CPET can address many more questions than an exercise test that only employs the electrocardiogram (ECG) to address the presence or absence of exercise induced myocardial ischemia.[8] While also employing electrocardiographic measurements, CPET also addresses a large number of questions about the physiology and pathophysiology of exercise. These questions are listed in Table 4.1, along with the measurements that can be used to address each question. Because the questions that can be addressed by integrative CPET are so comprehensive, testing at the beginning of a workup of a patient with exercise limitation, from any cause, would likely reduce the cost and time required to diagnose disorders of exercise intolerance.

Table 4.1

Questions Addressed by Cardiopulmonary Exercise Testing

Question	Disorder	Markers of abnormality[a]
Is exercise capacity reduced?	Any disorder	Maximal $\dot{V}O_2$ (panel 1)
Is the metabolic requirement for exercise increased?	Obesity	$\dot{V}O_2$–WR relationship (panel 1)
Is exercise limited by impaired O_2 flow?	Ischemic, myopathic, valvular, congenital heart disease	ECG; *AT*; $\Delta\dot{V}O_2/\Delta WR$; $\dot{V}O_2/HR$ (panels 1, 2, 3)
	Pulmonary vascular disease	$\Delta\dot{V}O_2/\Delta WR$; *AT*; $\dot{V}O_2/HR$; $\dot{V}E/\dot{V}CO_2$ (panels 1, 2, 3, 4, 6)
	Peripheral arterial disease	BP; $\Delta\dot{V}O_2/\Delta WR$; $\Delta\dot{V}CO_2/\Delta WR$ (panels 1, 5)
	Anemia, hypoxemia, elevated COHb	$\dot{V}O_2/HR$ (panels 1, 2, 3, 7)
Is exercise limited by reduced ventilatory capacity?	Lung; chest wall	BR; ventilatory response (panels 1, 4, 7, 9)
Is there an abnormal degree of $\dot{V}/\dot{Q}$ mismatching?	Lung disease; pulmonary vascular disease; heart failure	$P(A-a)O_2$; $P(a-ET)CO_2$; V_D/V_T; $\dot{V}E/\dot{V}CO_2$ at *AT* (panels 4, 6, 7)
Is there a defect in muscle utilization of O_2 or substrate?	Muscle glycolytic or mitochondrial enzyme defect	*AT*, R, $\dot{V}CO_2$; HR vs. $\dot{V}O_2$; lactate; lactate/pyruvate ratio (panels 1–3, 8)
Is exercise limited by a behavioral problem?	Psychogenic dyspnea; hysteria	Breathing pattern (panels 1, 7–9)
Is work output reduced because of poor effort?	Poor effort with secondary gain.	Increased HRR; increased BR; peak R < 1.0; normal *AT*, $P(A-a)O_2$ and $P(a-ET)CO_2$ (panels 1, 2, 3, 8, 9)

[a]Panel numbers refer to Figure 4.32.

Peak $\dot{V}O_2$, highest O_2 uptake measured; WR, work rate; *AT*, anaerobic threshold; $\Delta\dot{V}O_2/\Delta WR$, increase in $\dot{V}O_2$ relative to increase in work rate; $\dot{V}O_2/HR$, O_2 pulse; $\dot{V}E/\dot{V}CO_2$ at *AT*, ventilatory equivalent for CO_2 at anaerobic threshold; BR, breathing reserve, maximum voluntary ventilation minus ventilation at maximum exercise; $P(A-a)O_2$, alveolar–arterial P_{O_2} difference; $P(a-ET)CO_2$, arterial–end tidal P_{CO_2} difference; V_D/V_T, physiological dead space/tidal volume ratio; R, respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$); HRR, heart rate reserve, predicted maximum heart rate minus maximum exercise heart rate; COHb, carboxyhemoglobin.

WHEN SHOULD THE PATIENT UNDERGO CARDIOPULMONARY EXERCISE TESTING?

CPET is valuable if not essential in the following situations:

1. *Differential diagnosis*. When the cause of dyspnea or exercise limitation is uncertain (i.e., for differential diagnosis), integrative CPET can serve to define the specific organ system limiting gas transport. CPET performed at the beginning of diagnostic studies enables a more specific further workup.
2. *Disability evaluation*. By providing an objective assessment of exercise capacity and degree of impairment, CPET is of considerable, if not essential, value in disability evaluation.[56]
3. *Rehabilitation*. CPET provides information concerning the level of exercise that the patient can perform without undue stress. Thus, the test results guide the physician regarding exercise prescription in physical rehabilitation. It also furnishes quantitative evidence of the benefit of a rehabilitation program as well as the mechanism(s) of benefit. Improvement in exercise tolerance cannot be objectively assessed without CPET.[104]
4. *Assessing preoperative risk*. CPET is of value for preoperative evaluation of risk for patients about to undergo major surgery[18,55,72]; such testing enables the examiner to evaluate the stress that the cardiopulmonary system can undergo before anaerobic adenosine triphosphate (ATP) production, with resulting lactic acidosis, is recruited to complement aerobic ATP production. Predictably, CPET provides much more information about cardiovascular and pulmonary reserve during metabolic stress than measurements of cardiovascular and ventilatory function at rest.
5. *Grading severity of heart failure*. Peak $\dot{V}O_2$ and other measurements obtained from CPET have been found to be the useful predictors of survival time in patients with chronic heart failure.[17,29,37,45,75] A given cardiac le-

sion may have a different effect on different patients because of differences in the peripheral adaption to the cardiac abnormality and the effect of medications, hemoglobin content, and nutritional state. Because CPET addresses the body's global physiological adaptation to exercise, including compensatory mechanisms for the abnormal cardiac function, it has been valuable in grading and determining the cause of chronic (left ventricular) heart failure. To prioritize patients for heart transplantation,[49] CPET is an essential component of the patient's evaluation.

6. *Grading prognosis in chronic obstructive pulmonary disease.* Oga et al.[54] showed that peak O_2 uptake was a better predictor of survival in patients with chronic obstructive pulmonary disease (COPD) than the FEV_1 measurement. The recently completed National Emphysema Treatment Trials[25] also showed that death rate was highest in those patients with a reduced work rate, and that the latter was the critical determinant as to who might benefit from lung volume reduction surgery.
7. *Effectiveness of therapy.* Measurement of gas exchange has also been useful in evaluating functional improvement resulting from pacemakers in patients with heart block[85] and in objectively assessing various forms of medical therapy in patients with a variety of disorders.[41,99]
8. *Selecting patients for clinical trials.* While the selection of patients for clinical trials might be stipulated, it is usually subjectively based (e.g., New York Heart Association Functional Classification). Because there may be financial or other benefits to enrolling patients in clinical trials, the interpretation of patients' symptoms by physicians might be biased to include patients who would ordinarily be classified differently. CPET is useful for classifying the patient by function, enabling comparisons of therapeutic gains of patients with similar baseline impairments.

The measurements and functions that integrative CPET assesses are summarized in Table 4.2. Fortunately, most are noninvasive and can be performed in modern cardiology or cardiopulmonary function laboratories. Valuable insights into pathophysiology and grading of severity of impairment are provided by the measurements described in this chapter. The methods of measurement, calculations, and calibration and the method to assess accuracy are described in Appendix C and Chapter 6.

CPET is useful because it enables the examiner to (1) quantify the level of the subject's exercise limitation, (2) assess the adequacy of the performance of various components in the coupling of pulmonary to cellular gas exchange, (3) determine the organ system limiting exercise, and (4) determine the $\dot{V}O_2$ at which exercise limitation occurs. These evaluations can be addressed during short (approximately 10 minutes), progressive, non–steady-state exercise tests, rather than during a more prolonged exercise test with steps of relatively long duration. Prolonged testing is more likely to delay recovery of the patient, thereby making it more difficult for the investigator to repeat exercise testing if required. What makes CPET especially valuable is that it amplifies abnormalities in cardiopulmonary function and brings out abnormalities that are only present during exercise (e.g., exercise-induced myocardial ischemia).

MEASUREMENTS

Electrocardiographic Changes with Exercise

Myocardial ischemia results from an inadequate O_2 supply to the myocardium to meet the O_2 needed in support of increased cardiac work. When the myocardium becomes anaerobic, it alters its ionic permeability. Thus, the rate of reestablishing the electrical membrane potential during repolarization is slowed in the ischemic areas of the myocardium. This causes the T wave and ST segments to change acutely when the O_2 requirement for the increased cardiac work of exercise exceeds the availability of O_2 (Table 4.3). Because exercise causes the heart rate to increase and diastolic time to shorten, the time for coronary perfusion is decreased. Thus, coronary artery disease is more likely to be electrographically detected during exercise when the heart rate and the rate–pressure product are increasing.[13,28,34]

An increased frequency of ectopic beats, as the work rate increases, is also suggestive of myocardial ischemia. However, some subjects manifest occasional premature ventricular or atrial contractions at rest that disappear or become less frequent during exercise. Such ectopic beats appear to be benign and unrelated to a disturbance in the balance between myocardial O_2 availability and requirement because they are overridden by the sinus tachycardia of exercise.

In many instances, false-positive and borderline changes occur in the ECG when one relies solely on changes in the T wave and ST segments to detect exercise-induced myocardial ischemia. When these ECG changes are accompanied by myocardial dyskinesis, $\dot{V}O_2$ may fail to increase appropriately for the increasing work rate (WR). Thus, a reduction in $\Delta\dot{V}O_2/\Delta WR$ accompanied by ECG changes consistent with myocardial ischemia, with or without angina, strengthens the diagnosis of coronary artery disease involving a significant mass of myocardium. The diagnosis of ischemic heart disease is further supported if systemic blood pressure decreases or heart rate increases disproportionately to $\dot{V}O_2$ in the presence of ECG changes characteristic of myocardial ischemia during exercise.

Maximal Oxygen Uptake ($\dot{V}O_2$max) and Peak $\dot{V}O_2$

The body clearly has an upper limit for O_2 utilization at a particular state of fitness or training and the size of the muscle group employed in the work rate task. This

Table 4.2

Assessing Function with Physiologic Measurements

Measurements	Function
Electrocardiogram	Myocardial O_2 availability–requirement balance
$\dot{V}O_2$	Cardiac output × $C(a-\bar{v})O_2$
Peak $\dot{V}O_2$	Highest $\dot{V}O_2$ achieved during presumed maximal effort for an incremental exercise test (specific for type of work); may or may not equal $\dot{V}O_2$max
$\dot{V}O_2$max	Highest $\dot{V}O_2$ achievable as evidenced by failure for $\dot{V}O_2$ to increase despite increasing work rate (specific for type of work); highest cardiac output × $C(a-\bar{v})O_2$
$\Delta\dot{V}O_2/\Delta$WR	Aerobic contribution to exercise (low value suggests high anaerobic contribution); normally 10 mL/min/w
Cardiac output	Useful when evaluating hemodynamics
Anaerobic threshold (*AT*)	Highest $\dot{V}O_2$ that can be sustained without developing a lactic acidosis; important determinant of potential for endurance work (specific for form of work)
O_2 pulse	Product of SV and $C(a-\bar{v})O_2$; under conditions when SV is constant, change in O_2 pulse is proportional to change in $C(a-\bar{v})O_2$
Heart rate reserve (HRR)	Difference between predicted peak and measured heart rate at peak $\dot{V}O_2$
Arterial pressure	Detecting systemic hypertension, ventricular outflow obstruction, or myocardial failure (pulsus alternans or decreasing pressure with increasing WR)
$\dot{V}E = \dot{V}A + \dot{V}D$	$\dot{V}D$ is increased due to mismatching of $\dot{V}A$ to $\dot{Q}$. $\dot{V}A$ is increased inversely with decrease in $PaCO_2$, whether caused by a low CO_2 set point, metabolic acidosis, or hypoxemia.
BR = MVV − $\dot{V}E$ at max exercise, or (MVV − $\dot{V}E$ at max exercise)/MVV	Breathing reserve; theoretical additional $\dot{V}E$ available at cessation of exercise
Exercise VD/VT; $\dot{V}E/\dot{V}CO_2$ slope or ratio at the *AT* or VCP	Measures of mismatching of ventilation and perfusion
$P(a-ET)CO_2$	Detects high $\dot{V}A/\dot{Q}$ components of lung with mismatching of $\dot{V}A/\dot{Q}$
$P(A-a)O_2$	Increased in presence of mismatching of $\dot{V}A/\dot{Q}$, diffusion defect, or right-to-left shunt
Expired flow pattern	Useful for indicating presence of significant airflow obstruction
VT/IC	Fraction of the inspiratory capacity used in breathing
Immediate $\dot{V}O_2$ increase (phase I) in response to constant WR	Ability to increase pulmonary blood flow at start of exercise (phase I)
$\Delta\dot{V}O_2$ (6 − 3)	Proportional to lactate increase; positive if work rate is above *LT*
Decrease in $\dot{V}E$ during abrupt switch to 100% O_2 breathing	Contribution of the carotid body to ventilatory drive

WR, work rate; $\dot{V}E$, minute ventilation; HR, heart rate; VD, physiological dead space; SV, stroke volume; BR, breathing reserve; $C(a-\bar{v})O_2$, arterial–mixed venous O_2 content difference; MVV, maximal voluntary ventilation; VT, tidal volume; $\dot{V}D$, physiological dead space ventilation per minute; IC, inspiratory capacity; $\dot{V}A$, alveolar ventilation per minute; $\Delta\dot{V}O_2$ (6 − 3), difference between $\dot{V}O_2$ at 6 and 3 minutes during constant work rate exercise.

Table 4.3

Electrocardiographic Evidence of Myocardial Ischemia During Exercise

ST segment changes
T wave changes
Premature ventricular contractions that appear during exercise

is usually determined by the maximal cardiac output,[84] the arterial O_2 content, the fractional distribution of the cardiac output to the exercising muscle,[3] and the ability of the muscle to extract O_2.[86] The ventilatory capacity determines the upper limit of $\dot{V}O_2$ only when ventilation is insufficient to eliminate the CO_2 produced by aerobic metabolism and that resulting from bicarbonate buffering of lactic acid.[108]

Maximal aerobic power (i.e., maximal $\dot{V}O_2$ or $\dot{V}O_2$max) was originally defined as the $\dot{V}O_2$ at which performance of increasing levels of constant work rate exercise failed to increase $\dot{V}O_2$ by 150 mL per minute, despite increasing work rate.[84] This is illustrated in Figure 4.1A and shown experimentally in Figure 2.6. However, this definition has shortcomings because it is dependent on the exercise protocol and because 150 mL per min is a large fraction of the highest $\dot{V}O_2$ obtained in many patients.

The maximal $\dot{V}O_2$ may also be determined in a progressively increasing exercise test by observing that $\dot{V}O_2$ fails to increase normally relative to the increase in work rate (<10 mL/min/W) just before the subject fatigues (Figs. 4.1 and 4.2). However, flattening of the $\dot{V}O_2$–work rate relationship, as peak $\dot{V}O_2$ is approached, is often not seen in progressively increasing exercise tests (see Fig. 4.2). This highest $\dot{V}O_2$ is called the peak $\dot{V}O_2$ and is the terminology used to describe the highest $\dot{V}O_2$ achieved in an increasing work-rate test. The highest $\dot{V}O_2$ might also be regarded as the maximal $\dot{V}O_2$ when it fails to increase normally over the last 60 seconds of exercise before the subject stops exercise because of fatigue—that is, $\dot{V}O_2$ fails to increase further despite an increase in work rate (see Fig. 4.2). Although the peak $\dot{V}O_2$ does not satisfy the definition of the maximal $\dot{V}O_2$ determined from repeated constant work-rate tests, it is usually equal to the actual $\dot{V}O_2$max in normal subjects. The distinction between $\dot{V}O_2$max and peak $\dot{V}O_2$ is diagrammed in Figure 4.1.

In summary, a similar $\dot{V}O_2$ during a series of supramaximal constant work-rate tests or progressively increasing work-rate tests shows that a maximal $\dot{V}O_2$ ($\dot{V}O_2$max) has, in fact, been attained for the work rate performed. In studies in normal subjects performing

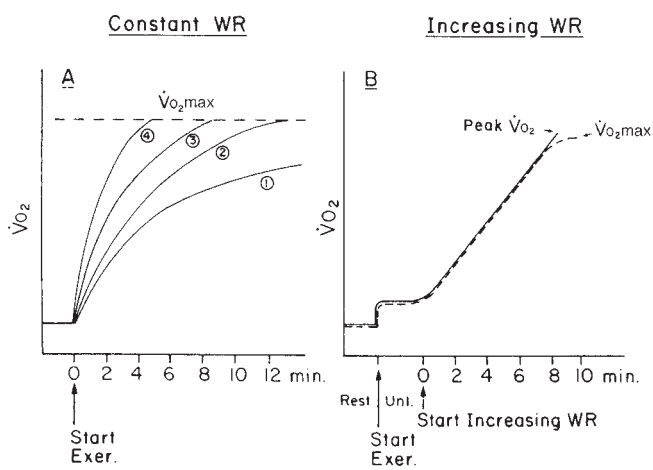

FIGURE 4.1. **A:** Determining the maximal $\dot{V}O_2$ ($\dot{V}O_2$max) from supramaximal work-rate tests. The time course of $\dot{V}O_2$ following the onset of exercise is shown for progressively higher work rates. For work rate 1, the $\dot{V}O_2$ asymptote is below $\dot{V}O_2$max. Work rate 2 reaches a $\dot{V}O_2$ that is the same as the highest $\dot{V}O_2$ reached by work rates 3 and 4. Because the maximum $\dot{V}O_2$ is the same for work rates 2, 3, and 4, this identifies $\dot{V}O_2$max for the form of exercise studied. **B:** Distinguishing between $\dot{V}O_2$max and "peak" or "maximum" $\dot{V}O_2$ from a maximal-effort incremental exercise test. When the subject's maximum tolerable work rate results in a flattening of the $\dot{V}O_2$–work rate slope, this is the subject's maximal $\dot{V}O_2$, or $\dot{V}O_2$max. When the $\dot{V}O_2$ does not slow its rate of rise with increasing work rate, but the subject has reached his or her maximum tolerable work rate, this is the peak (or maximum) $\dot{V}O_2$ during the test.

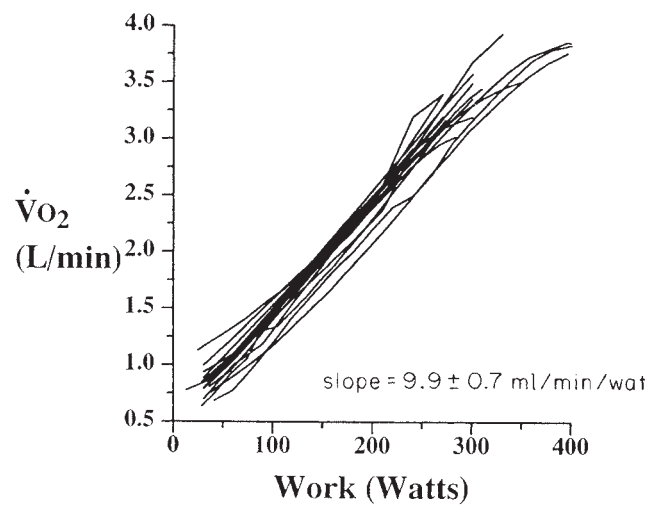

FIGURE 4.2. The effect of work rate on oxygen uptake ($\dot{V}O_2$) during progressively increasing work-rate cycle ergometer exercise for 17 normal subjects. The average regression slope and standard deviation for the subject population are given in the equation in the figure. The slope is consistent among subjects but is displaced upward depending on body weight, as shown in Figure 2.7. (From Wasserman K, Sue DY. Coupling of external to cellular respiration. In: Wasserman K, ed. *Exercise Gas Exchange in Heart Disease*. Armonk, NY: Futura Publishing; 1996:1–15, with permission.)

progressively increasing exercise to the point of fatigue or dyspnea, only about one-third of normal subjects making maximal effort reach a plateau in $\dot{V}O_2$ (see Fig. 4.2). After reaching their peak $\dot{V}O_2$, many subjects cannot endure the discomfort long enough to achieve a work rate–related plateau in $\dot{V}O_2$. (See the power-duration curve in Chapter 2.) For normal children, the regression equations and scaling factors for those who did not reach a plateau were indistinguishable from those children who reached a plateau.[20]

A plateau in $\dot{V}O_2$ may also fail to occur during a progressively increasing work-rate test when the subject stops exercising because of leg or chest pain, shortness of breath, mechanical limitation to breathing, or lack of motivation. In these instances, the peak $\dot{V}O_2$ will not satisfy the definition of $\dot{V}O_2$max.

Note that at high-intensity exercise, the $\dot{V}O_2$ does not reflect all the high-energy phosphate expended by the subject. It does not account for the energy generated when high-energy phosphate is split from phosphocreatine (PCr) or for the ATP generated from anaerobic glycolysis, resulting in a net increase in lactate. The latter becomes increasingly important as an energy source as work rate increases above the anaerobic threshold (*AT*).[23]

A progressively increasing work-rate exercise test, as illustrated in Figures 4.1B and 4.2, has several advantages:

1. The test starts out at a relatively low work rate, so that it does not require the abrupt application of great muscle force or a sudden, large cardiorespiratory stress.
2. The $\dot{V}O_2$max or peak $\dot{V}O_2$ can be determined from an exercise test in which the period of increasing work rate lasts only 8 to 12 minutes.
3. The subject is stressed for only a few minutes at relatively high work rates.
4. The $\dot{V}O_2$–work rate relationship can be determined if the ergometry work rate can be measured, such as for the cycle.

To obtain the best data for interpreting the measured responses to a progressively increasing work-rate exercise test, the work-rate increments should be uniform in magnitude and duration. This means that the ergometer work rate must be accurately calibrated and increase, linearly.

The peak $\dot{V}O_2$ is the first measurement to be examined because it establishes whether the patient's physiologic responses allow normal maximal aerobic function. Other measurements are then used to differentiate the cause of exercise limitation whether or not the subject reaches his or her predicted peak $\dot{V}O_2$.

Oxygen Uptake and Work Rate

Although $\dot{V}O_2$ measurements are made from respired gas measured at the mouth, the increase in $\dot{V}O_2$ reflects O_2 utilization by the muscle cells performing the work of exercise. The $\dot{V}O_2$–work rate relationship describes how much O_2 is utilized by the exercising subject in relation to the quantity of external work performed. Because it gives important information concerning the coupling of external to internal (cellular) respiration, it is valuable to graph $\dot{V}O_2$ and work rate as a function of time and measure the ability of $\dot{V}O_2$ to track the increase in work rate. The coupling of external respiration to cellular respiration is the responsibility of the cardiovascular system. Therefore, disease of some component of the cardiovascular system will result in an abnormal pattern of gas exchange for increasing work-rate exercise, characteristic of that component.

Pattern of the $\dot{V}O_2$ Response to Increasing Work Rate ($\Delta\dot{V}O_2/\Delta$WR) in Normal Subjects, Obese Patients, and Patients with Specific Cardiovascular Abnormalities

Normal Subjects

$\dot{V}O_2$ increases smoothly when cycle ergometer work rate is increased in a continuous ramp pattern or in equal steps of 1-minute duration (Fig. 4.3). This type of protocol has advantages in the ease with which the patient perceives the addition of work rate during testing. Increasing work rate in 2- or 3-minute steps results in relatively large abrupt changes in work rate, and the increase in $\dot{V}O_2$ at each interval is a step pattern (see Fig. 4.3).[114] Because the time constant for $\dot{V}O_2$ at work intensities below the *AT* is 35 to 45 seconds in healthy subjects, steps at 1-minute increments give smooth increases in $\dot{V}O_2$. Thus, the slope of increase in $\dot{V}O_2$ as a function of work rate can be calculated with either the ramp or 1-minute step increase in work rate.[114] As shown in Chapter 2 and Figure 4.2, the normal $\Delta\dot{V}O_2/\Delta$WR is equal to 10 mL/min/W. For 3-minute step increases in work rate, the step appearance in $\dot{V}O_2$ is damped at the higher work intensity because of the progressive slowing of $\dot{V}O_2$ kinetics as the subject approaches $\dot{V}O_2$max.[115] Therefore, the loss of the step change in $\dot{V}O_2$ depends on fitness (Fig. 4.4).

Upward Displacement of $\dot{V}O_2$ as a Function of Work Rate in Obesity

The position of the $\dot{V}O_2$–work rate relationship depends on body weight (Fig. 4.5A). Obese subjects require increased $\dot{V}O_2$ to do a given amount of external work (see the section *Oxygen Cost of Work* in Chapter 2). This is due to the added O_2 cost to move the limbs during cycling ergometry and the cost of moving the entire body during treadmill exercise. Based on two separate studies of cycle ergometer exercise on adults, the $\dot{V}O_2$ was found to be displaced upward by approximately 5.8 mL/min/kg of body weight[31,96] during unloaded cycling at 60 rpm. Although

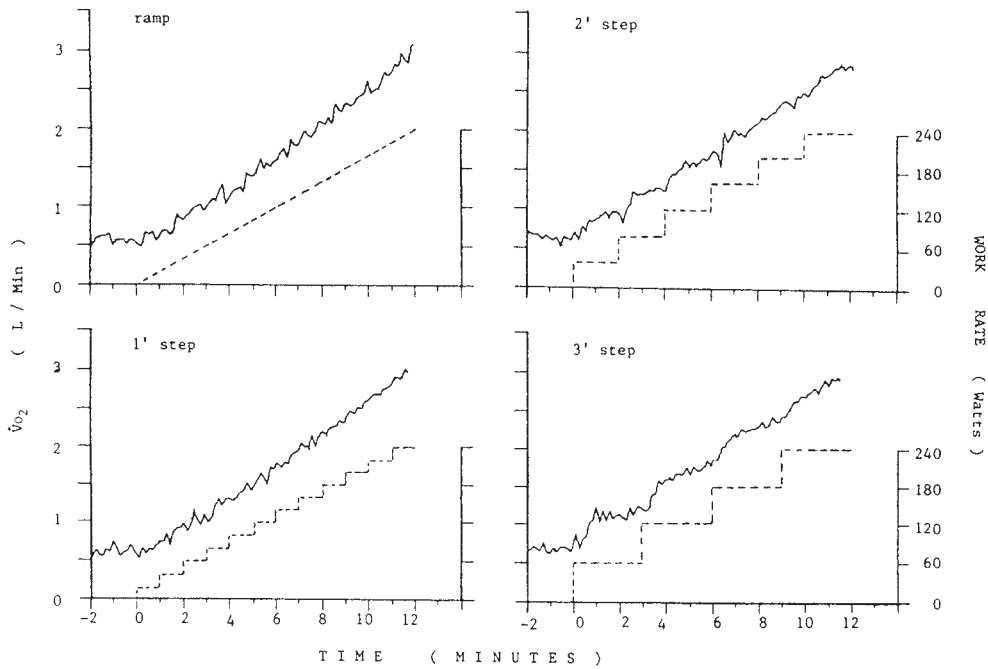

FIGURE 4.3. $\dot{V}O_2$ response in a single subject to four different protocols: ramp and 1-, 2-, and 3-minute steps. The dashed lines show the administered work rate and pattern of work rate increase with time. The $\dot{V}O_2$ data are the average of 9-second periods. (From Zhang YY, Johnson MC, Chow N, et al. Effect of exercise testing protocol on parameters of aerobic function. *Med Sci Sports Exerc.* 1991;23:625–630, with permission.)

upwardly displaced, the $\dot{V}O_2$–work rate relationship in obesity parallels that of the normal-weight subject during cycle ergometry.

For treadmill exercise, a predictable adjustment for body weight is not possible because of complex mechanical factors such as varying center of gravity as the angle of the treadmill is changed, the variable length of the stride as the speed and grade are altered, and the tendency of the subject to hold on to stationary objects for support or balance during the test. These variables make it difficult to estimate the subject's actual power output during treadmill ergometry. Recently, Porszasz et al.[59] described how to linearize a treadmill exercise protocol. We recommend it for treadmill ergometry. In addition, to avoid the temptation of holding on to the treadmill railing for balance, we advise our patients to rest the back of the hand(s) on the treadmill railing.

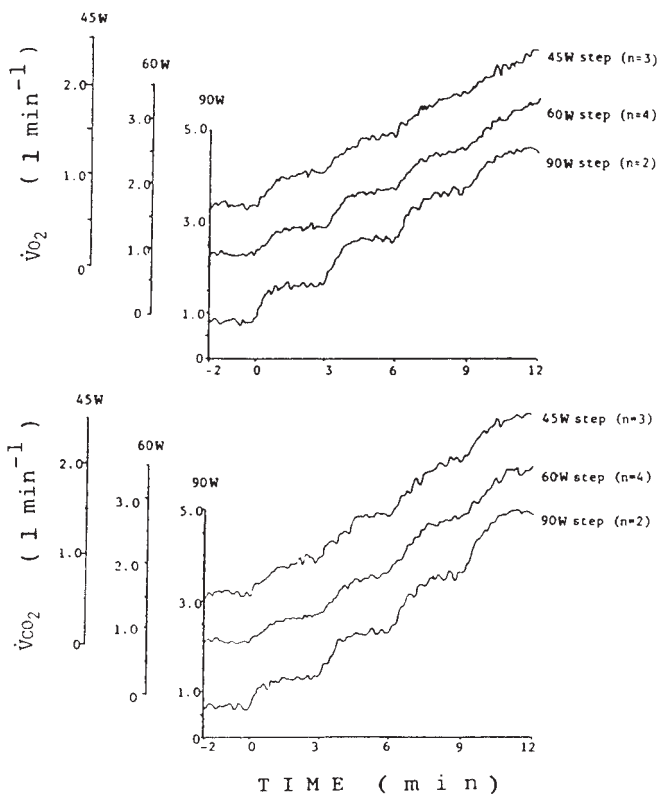

FIGURE 4.4. The average time course of $\dot{V}O_2$ and $\dot{V}CO_2$ for each quarter of a subject's work capacity, assessed in 3-minute work rate steps, is shown for normal subjects at three fitness levels. The greater the size of the step increase in work rate (90-, 60-, or 45-W steps), the greater the subject's fitness ($\dot{V}O_2$peak). At higher work rates, the gas exchange kinetics slow and thereby appear to be more damped. Because the subjects with the larger step increases are more fit, their kinetics are faster and there is less damping of gas exchange. (From Zhang YY, Johnson MC, Chow N, et al. The role of fitness on $\dot{V}O_2$ and $\dot{V}CO_2$ kinetics in response to proportional step increases in work rate. *Eur J Appl Physiol.* 1991;63:94–100, with permission.)

Slope of $\dot{V}O_2$ as a Function of Work Rate ($\Delta\dot{V}O_2/\Delta WR$)

The slope of $\dot{V}O_2$ as a function of work rate is important because it measures the aerobic work efficiency. The $\dot{V}O_2$-WR slope for the ramp or 1-minute incremental cycle ergometer progressively increasing work-rate test was found to be 10.2 ± 1.0 mL O_2/min/W for normal subjects by Hansen et al.[31] and 9.9 ± 0.7 mL/min/W by Wasserman and Sue[94] (see Fig. 4.2). These values are similar to the

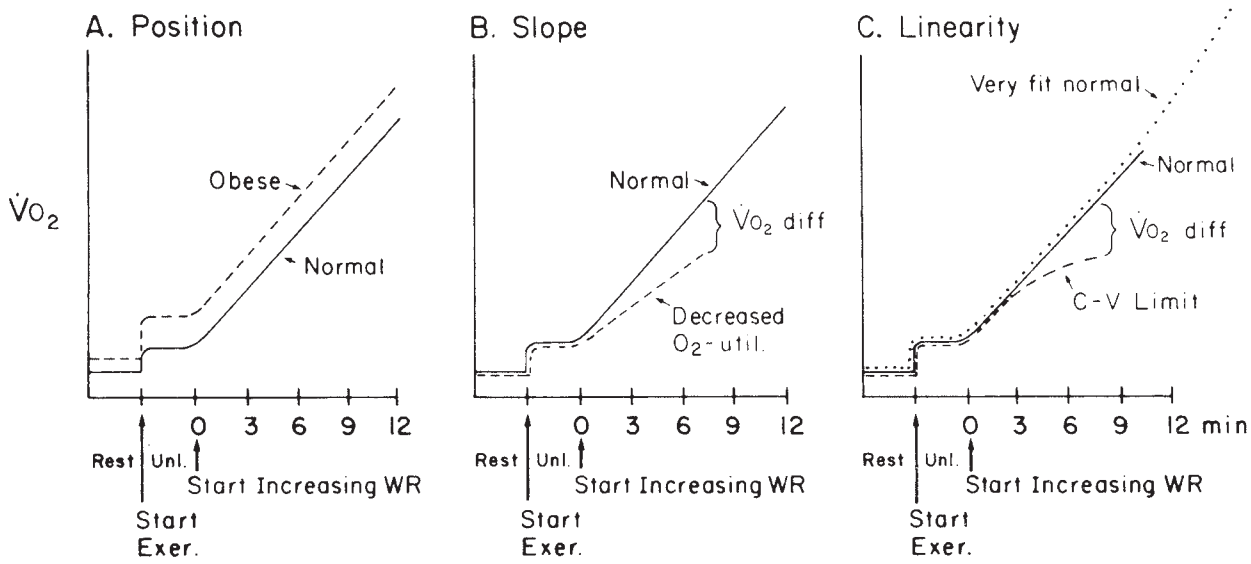

FIGURE 4.5. Position displacement **(A)**, slope **(B)**, and linearity **(C)** of the $\dot{V}O_2$–work rate relationship. Obesity displaces the $\dot{V}O_2$–work rate relationship upward, but the slope is unchanged **(A)**. A decreased slope of the $\dot{V}O_2$–work rate relationship **(B)** reflects inadequate O_2 availability to the exercising muscles, such as when peripheral blood flow is impaired. The linearity of the $\dot{V}O_2$–work rate relationship **(C)** can be altered in patients with cardiovascular diseases (slope becomes more shallow) because of impaired O_2 flow to the exercising muscles, or in very fit people (slope becomes steeper; see text). The difference between the expected $\dot{V}O_2$ for the work rate performed and the actual $\dot{V}O_2$ at the maximum work rate of the subject is referred to as the $\dot{V}O_2$ difference.

value of 10.1 mL O_2/min/W previously obtained from steady-state measurements in sedentary subjects.[96] In 12 trained cyclists, Riley et al.[62] obtained an average slope of 11.5 mL O_2/min/W with a standard deviation of 0.78, suggesting that athletes may have a slightly higher $\Delta\dot{V}O_2/\Delta$WR than nonathletes.

Linearity of $\dot{V}O_2$ as a Function of Work Rate

Because O_2 uptake kinetics are a more complex function of work rate than a single exponential at work rates above the *AT*,[44,106] the slope of the $\dot{V}O_2$–work rate relationship is not necessarily the same above the *AT* as below the *AT* (see Fig. 4.5C). If the rate of increase in work rate is rapid relative to the subject's degree of fitness, then a relatively large proportion of energy generated is from anaerobic sources and the slope would be expected to become more shallow (60 W per min; see Figs. 2.27 and 2.29). In contrast, when the rate of increase in work rate is slow, several factors may account for an augmented O_2 uptake and thereby cause the $\dot{V}O_2$–work rate slope to steepen above the *AT*:

1. The use of additional muscle groups when performing heavy exercise (e.g., pulling on cycle handlebars during leg cycling to brace the trunk on the ergometer as the pedals get harder to turn)
2. A nonlinear increase in the work of breathing as high levels of ventilation are reached
3. The O_2 cost of lactate conversion to glycogen (Cori cycle) by tissues actively involved in gluconeogenesis (primarily liver)
4. The recruitment of less efficient muscle fibers (type IIx) at high work rates

However, this steepening of the $\dot{V}O_2$ response to exercise is rarely pathological. It has been attributed to increased work of breathing in some patients with COPD.[96]

If the rate of increase in work rate were relatively slow for a fit subject, then any or all four factors noted above could contribute to the increase in $\dot{V}O_2$ relative to work rate increase, above the *AT*.[33,106] In contrast, rapid increases in work rate result in a sizable fraction of anaerobic work above the *AT* (as assessed by a high rate of lactate increase), and $\dot{V}O_2$ would therefore increase more slowly relative to the work rate increase in the above-*AT* range of work.[32] Thus, in the same subject, the $\dot{V}O_2$–work rate relationship above the *AT* can be more steep (slow work rate increase) or less steep (rapid work rate increase) than below the *AT*. However, the peak $\dot{V}O_2$ is not systematically affected by the rate of work rate increase. In general, work rate increments of 15 to 25 W per minute in normal men and 10 to 20 W in normal women give a similar rate of rise in $\dot{V}O_2$ both above and below the *AT*. A method for selecting the work rate increment for progressively increasing work rate exercise testing of normal subjects and patients is described in Chapter 6.

Can $\dot{V}O_2$ or Mets Be Predicted from the Work Rate?

Some laboratories estimate $\dot{V}O_2$ from work rate during exercise rather than measuring $\dot{V}O_2$ directly. This practice is inaccurate and should be discouraged. A unit called a *met* was derived from the average resting $\dot{V}O_2$ for a 70-kg, 40-year-old man. It is equal to 3.5 mL/min/kg of body weight. By assuming a fixed relationship between the ergometer work rate and the $\dot{V}O_2$, some laboratories report an estimate of $\dot{V}O_2$ from the ergometer work rate. After obtaining this estimated $\dot{V}O_2$ and expressing it per kilogram of body weight, the $\dot{V}O_2$ per kilogram is divided by 3.5 to obtain the number of mets performed by the subject.

However, under many conditions, $\dot{V}O_2$ cannot be accurately predicted from the estimated work rate for the reasons summarized in Table 4.4. If $\dot{V}O_2$ does not increase linearly with increasing work rate, as is common in patients with cardiovascular diseases, $\dot{V}O_2$ cannot be estimated from work rate (see Fig. 4.5C and the cardiovascular cases in Chapter 10).[39] Thus, using work rate to calculate $\dot{V}O_2$ or mets will usually lead to overestimates in these patients.

In addition, work rate fails to predict $\dot{V}O_2$ if the obesity factor is not taken into account. This factor is often ignored or incorrect estimates of the effect of body weight are used. The $\dot{V}O_2$ to perform a given amount of external work will be higher in an obese subject than in a lean subject because of the need to expend additional energy to move a large body when effecting external work. For cycle ergometer work, we have found that the O_2 cost of cycling at 60 rpm on an unloaded ergometer is an additional 5.8 mL per min for each kilogram body weight.[31,96]

Appendix C and Chapter 6 should be reviewed for methods of assuring accuracy in gas exchange measurements and ergometer calibration.

Cardiac Output and Stroke Volume

Cardiac output measurement may be useful when trying to assess whether the patient's reduced O_2 uptake is due to reduced O_2 transport or failure of the muscles to extract O_2 for whatever cause. However, cardiac output measurement by itself, even if accurate, may not reveal whether cardiac output is adequate for the work rate performed. The major concern of exercise testing should be to determine whether the circulation is capable of providing the exercise-stressed muscles with enough oxygen. To answer this important question, measurement of the *AT* and $\Delta\dot{V}O_2/\Delta WR$ during a progressively increasing work-rate test, as well as measurement of the $\dot{V}O_2$ and $\dot{V}CO_2$ kinetics during a constant work-rate test, may be more useful. Because all of these measurements are made noninvasively with CPET, they can be repeated easily.

Table 4.4

Conditions in Which Work Rate Fails to Predict $\dot{V}O_2$

$\dot{V}O_2$ fails to increase linearly with work rate
Obesity
Valvular heart disease
Coronary artery disease
Cardiomyopathy
Peripheral arterial disease
Pulmonary vascular disease
Faulty ergometer calibration

Cardiac Output Measurement

Thermodilution

If a thermistor-tipped catheter is introduced into the pulmonary artery, the cardiac output can be determined from a thermodilution curve after the injection of iced saline into the lumen of the catheter that opens into the right atrium. From this curve and the volume of iced saline injected, blood flow through the pulmonary artery can be calculated.[102]

Indirect Fick Method Using $\dot{V}CO_2$ and Estimated $C\bar{v}CO_2$

Estimates of cardiac output during exercise are sometimes made with the indirect Fick method:

$$\text{Cardiac output} = \dot{V}CO_2/C(\bar{v} - a)CO_2$$

from a measurement of $\dot{V}CO_2$ and an estimate of arterial PCO_2 ($PaCO_2$) from end-tidal PCO_2 ($PETCO_2$) and mixed venous PCO_2 by the CO_2 rebreathing method.[35] (See Appendix A for definitions of symbols and Appendix C for a description of the rebreathing method.)

This approach has many potential errors. First, estimation of $PaCO_2$ from $PETCO_2$ measurements, as commonly done, is unreliable, especially in patients.[36,79] $PETCO_2$ is less than $PaCO_2$ in patients with lung disease, heart failure, and pulmonary vascular disease and greater than $PaCO_2$ in normal subjects (see Chapter 5). Second, the assumption is made that mixed venous CO_2 content can be determined accurately from mixed venous PCO_2 using a standard CO_2 dissociation curve in which blood CO_2 content is plotted as a function of blood PCO_2. If the work is above the *AT*, however, the CO_2 content will be decreased for the same mixed venous PCO_2 as that below the *AT* because of a shift downward in the subject's CO_2 dissociation curve.[64] This shift downward results from the decrease in CO_2 content for a given PCO_2 of blood because HCO_3^- dissociates when it buffers lactic acid. Third, the assumption is made that the CO_2 dissociation curve

is linear, although in reality it gets less steep the higher the P_{CO_2}.

Sun et al.[83] determined the P_{CO_2} and CO_2 content of mixed venous blood at all levels of exercise and found that mixed venous CO_2 content increased, although nonlinearly with work rate, up to the *AT* (see Chapter 3). Above the *AT*, $P\bar{v}CO_2$ rose steeply but mixed venous CO_2 content decreased. This is due to the decrease in HCO_3^- consequent to its buffering of lactic acid (the pH effect). This effect cannot be estimated without direct mixed venous blood gas and pH measurements. Because of this phenomenon, the CO_2 rebreathing method for determining mixed venous CO_2 content, particularly above the *AT*, cannot be accurate.

Direct Fick Method

From the measurement of $\dot{V}O_2$ and the simultaneous measurement of arterial and mixed venous O_2 content, cardiac output can be determined from the direct Fick equation:

$$\text{Cardiac output} = \dot{V}O_2 / C(a - \bar{v})O_2$$

Mixed venous ($\bar{v}$) and systemic arterial (a) O_2 contents are determined from a catheter in the pulmonary and systemic artery, respectively. This method represents the gold standard for cardiac output measurement. Sun et al.[83] compared the direct Fick method using O_2 as the test gas with that using CO_2. The cardiac outputs were very similar, on average, although the variability in the measurements was greater using CO_2 as the test gas than when using O_2.

Noninvasive Cardiac Output and Stroke Volume by the Fick Principle

Stringer et al.[77] pointed out that cardiac output can be calculated during exercise, noninvasively, by the Fick principle with a reliability as good as generally reported by other methods. The measurement takes advantage of the knowledge that percent of maximal O_2 extraction is consistent at the *AT* and peak $\dot{V}O_2$ in normal subjects[77] and heart failure patients regardless of severity of impairment.[100] By taking hemoglobin concentration into account and the percent arterial saturation, $C(a - \bar{v})O_2$ can be determined by applying the Fick principle. The key is that mixed venous percent O_2 extraction is consistent at peak exercise and at *AT* (Table 4.5 and Fig. 4.6). $C(a - \bar{v})O_2$ content differences for normal subjects and heart failure patients are shown at rest, *AT*, and peak $\dot{V}O_2$ in Table 4.5. Although the standard deviation is relatively small, the $C(a - \bar{v})O_2$ values could be further improved by taking into account the hemoglobin concentration, arterial O_2 saturation, carboxyhemoglobin concentration, and fitness as described in Table 4.6. The accuracy of the stroke volume and cardiac output measurement is less affected by $C(a - \bar{v})O_2$ as peak $\dot{V}O_2$ is approached (Fig. 4.7). The basic equations used in the calculations of Figure 4.7 are:

$$\text{Cardiac output: } CO = \dot{V}O_2 / C(a - \bar{v})O_2$$

$$\text{Stroke volume: } SV = O_2\text{–pulse} / C(a - \bar{v})O_2$$

$$CaO_2 = \text{Fractional art sat} \times 1.34 \times [\text{Hb}]$$

Table 4.5

Arteriovenous O_2 Difference and Extraction Ratio ± Standard Deviation at Rest, Anaerobic Threshold (*AT*), and Peak $\dot{V}o_2$

	$\dot{V}o_2$ (L/min)	Arteriovenous O_2 difference (mL/dL)	Extraction ratio[a]
Normal men[b]			
Rest		6.14 ± 1.7	0.30 ± 0.09
AT	1.84 ± 0.36	11.3 ± 0.87	0.53 ± 0.04
Peak $\dot{V}O_2$	3.77 ± 0.61	16.2 ± 1.2	0.74 ± 0.07
Chronic heart failure[c]			
Rest	0.28 ± 0.07	7.8 ± 2.6	0.43 ± 0.11
AT	0.83 ± 0.25	13.0 ± 2.4	0.68 ± 0.09
Peak $\dot{V}O_2$	1.26 ± 0.39	15.0 ± 2.7	0.77 ± 0.07

[a]Extraction ratio equals fractional difference between CaO_2 and $C\bar{v}o_2$.
[b]Data from Stringer W, Hansen J, Wasserman K. Cardiac output estimated non-invasively from oxygen uptake ($\dot{V}O_2$) during exercise. *J Appl Physiol.* 1997;82:908–912.
[c]Data from Agostoni PG, Wasserman K, Perego G, et al. Stroke volume (SV) measured, non-invasively at anaerobic threshold (*AT*) in heart failure (HF). *Am J Respir Crit Care Med.* 1997;155:A171.

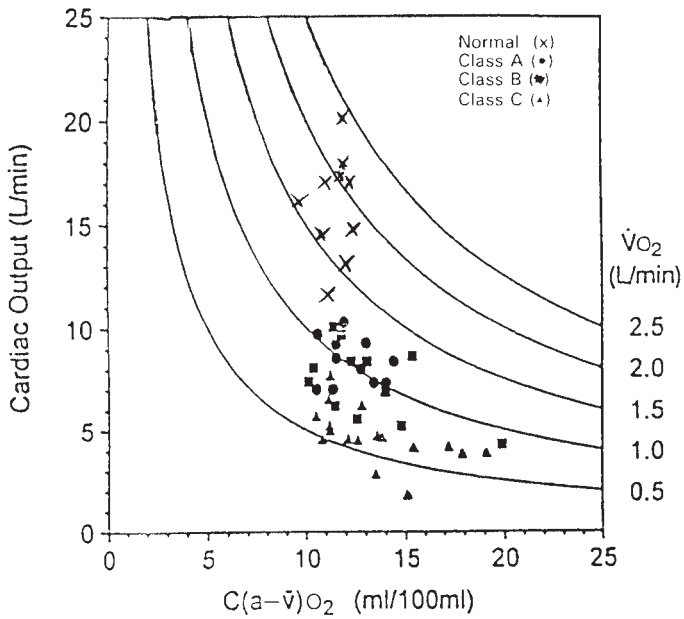

FIGURE 4.6. Cardiac output (calculated by the direct Fick method) is plotted as a function of arteriovenous O_2 difference [$C(a - \bar{v})O_2$] at the anaerobic threshold (*AT*) for normal and heart failure subjects in physiological class A (peak $\dot{V}O_2$ >20 mL/min/kg), B (peak $\dot{V}O_2$ = 15–20 mL/min/kg), and C (peak $\dot{V}O_2$ = 10–15 mL/min/kg). Superimposed are $\dot{V}O_2$ isopleths. See the text for further discussion of the application of these plots in estimating cardiac output. (Data taken from Stringer W, Hansen J, Wasserman K. Cardiac output estimated non-invasively from oxygen uptake (V_{O_2}) during exercise. *J Appl Physiol.* 1997;82:908–912 and from Agostoni PG, Wasserman K, Perego G, et al. Stroke volume (SV) measured non-invasively at anaerobic threshold (*AT*) in heart failure (HF). *Am J Respir Crit Care Med.* 1997;155:A171.)

The following are equations for the range of arterial-venous O_2 difference at rest, *AT*, and peak $\dot{V}O_2$, if [Hb] = 15 gm per dL:

Rest:

% art O_2 Hb = 0.96 × 1.34 × 15 = 19.3 mL/100 mL blood

% ven O_2 Hb = 0.70 × 1.34 × 15 = 14.1 mL/100 mL blood

$$C(a - \bar{v})O_2 = 5.2 \text{ mL/dL}$$

Anaerobic threshold:

% art O_2 Hb = 0.96 × 1.34 × 15 = 19.3 mL/100 mL blood

% ven O_2 Hb = 0.40 × 1.34 × 15 = 8.0 mL/100 mL blood

$$C(a - \bar{v})O_2 = 11.3 \text{ mL/dL}$$

Peak $\dot{V}O_2$

% art O_2 Hb = 0.96 × 1.34 × 15 = 19.3 mL/100 mL blood

% ven O_2 Hb = 0.20 × 1.34 × 15 = 4.0 mL/100 mL blood

$$C(a - \bar{v})O_2 = 15.3 \text{ mL/dL}$$

See Figure 4.7 for effect of hemoglobin concentrations of 15 and 12 g per dL, with normal arterial O_2 saturation, on cardiac output and stroke volume.

Table 4.6.

Estimation of Arteriovenous Oxygen Difference [$C(a - \bar{v})O_2$] at Peak Exercise

Hb (g/100 mL)[a]	O_2 capacity (mL/100 mL)	Arterial O_2 saturation (%)	Mixed venous O_2 saturation (%)	Arterial O_2 concentration (mL/100 mL)	Mixed venous O_2 concentration (mL/100)	$C(a - \bar{v})O_2$ (mL/100 mL)[b]
16	22.5	96	24	21.4	5.4	16.0
15	21.1	96	24	20.0	5.0	15.0
14	19.7	96	24	18.7	4.7	14.0
13	18.3	96	24	17.4	4.4	13.0
12	16.9	96	24	16.0	4.0	12.0
11	15.5	96	24	14.7	3.7	11.0
10	14.1	96	24	13.4	3.4	10.0

[a]The left column identifies the resting hemoglobin concentration. The hemoglobin concentration at peak exercise is considered to be 5% higher than the resting hemoglobin—that is, a fitness factor of 1.05 (see text for definition). The carboxyhemoglobin concentration is assumed to be 1%.
[b]Modifications: (1) If the person is very unfit, decrease the $C(a - \bar{v})O_2$ (right column) by up to 6%; if the person is very fit, increase the $C(a - \bar{v})O_2$ by up to 6%. (2) Reduce the $C(a - \bar{v})O_2$ by 1% for each 1% increase in carboxyhemoglobin above 1%. (3) Reduce the $C(a - \bar{v})O_2$ by 1% for each 1% decrease in arterial oxyhemoglobin saturation below 96%.

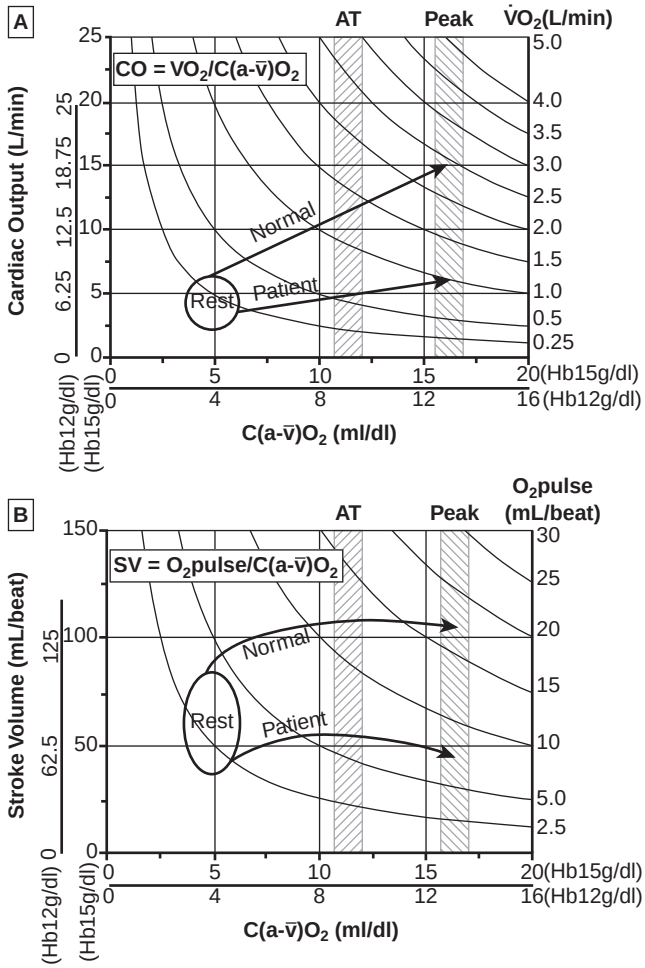

FIGURE 4.7. Cardiac output **(A)** and stroke volume **(B)** determined from calculated $C(a-\bar{v})O_2$ at different levels of hemoglobin concentration and measured $\dot{V}O_2$ at the anaerobic threshold (*AT*) and peak $\dot{V}O_2$. Diagram showing **(A)** the determination of cardiac output from $\dot{V}O_2$ and arterial-venous O_2 difference [$C(a-\bar{v})O_2$] and **(B)** stroke volume from O_2 -pulse ($\dot{V}O_2$/HR) and ($C(a-\bar{v})O_2$) using the Fick principle. The *x* axis displays the $C(a-\bar{v})O_2$ differences for hemoglobin concentrations of 15 and 12 g per dL, assuming normal arterial oxyhemoglobin saturation (see text for oxyhemoglobin desaturation correction). $C(a-\bar{v})O_2$ percent extractions at the *AT* and peak have been shown to be similar for heart failure patients, regardless of severity, and normal subjects (see Fig. 4.6). To facilitate use of these figures to estimate cardiac output and stroke volume at the *AT* and peak exercise, vertical bars are shown in the ranges of $C(a-\bar{v})O_2$ at *AT* and peak $\dot{V}O_2$ from the cited references. The pattern of change in cardiac output and stroke volume from rest to the *AT* and peak $\dot{V}O_2$ for a normal middle-aged male subject and a male patient with heart failure of equal age and size are represented by the labeled arrows on the graphs that derive cardiac output **(A)** and stroke volume **(B)**.

Values between these hemoglobin concentrations can be interpolated.

Table 4.6 and its footnotes show the effect of hemoglobin concentration in more detail, as well as the additional effects of arterial oxyhemoglobin decrease, carboxyhemoglobin increase, and fitness on $C(a-\bar{v})O_2$. The equations for the effect of hemoglobin concentration and arterial oxyhemoglobin saturation on $C(a-\bar{v})O_2$ are:

At peak: [Hb] × 1.34 × (fraction art sat − 0.2)

At *AT*: [Hb] × 1.34 × (fraction art sat − 0.4)

At rest: [Hb] × 1.34 × (fraction art sat − 0.70)

Hemoglobin concentration is generally the major factor. Chapter 9 includes a discussion of the modifying factors, which are important to consider.

The determination of cardiac output is made from the $\dot{V}O_2$ measurement alone, at work rates at which $C(a-\bar{v})O_2$ can be estimated with relative accuracy, such as at *AT* and peak $\dot{V}O_2$. It was shown that $C(a-\bar{v})O_2$ increases relatively linearly to peak $\dot{V}O_2$ in normal subjects and patients with heart failure,[100] achieving a value of approximately 75% to 80% at peak $\dot{V}O_2$. Agostoni et al.[1] found that patients with more severe chronic heart failure, on average, had higher values for $C(a-\bar{v})O_2$ at the *AT*. However, they had similar values to normal subjects at peak $\dot{V}O_2$ (see Table 4.5). From the shape of the $\dot{V}O_2$ curves shown in Figure 4.6, variability in the $C(a-\bar{v})O_2$ has less influence on the cardiac output determination, in absolute terms, as $C(a-\bar{v})O_2$ increases and as $\dot{V}O_2$ decreases.

Direct Fick cardiac outputs calculated from directly measured $\dot{V}O_2$ and arterial and mixed venous oxyhemoglobin concentrations at *AT* are plotted as a function of $C(a-\bar{v})O_2$ for normal subjects[77] and in patients with stable chronic heart failure.[1] Normal young men had a standard deviation for $C(a-\bar{v})O_2$ of 7.6% and 7.4% and for extraction ratio of 7.5% and 9.4% at the *AT* and peak $\dot{V}O_2$, respectively (see Table 4.5).[77] Patients with heart failure had a standard deviation for an extraction ratio at *AT* and peak $\dot{V}O_2$ of 13% and 9%, respectively (see Table 4.5).[1] The standard deviation for $C(a-\bar{v})O_2$ at the *AT* for the patients was higher than that for normal subjects because these values increased as the cardiac output decreased (see Fig. 4.6). However, no values for $C(a-\bar{v})O_2$ were below 10 mL per dL.

For the heart failure subjects, the higher $C(a-\bar{v})O_2$ values in the distribution are dominated by the more exercise limited patients. From Figure 4.6, it is evident that the variability in $C(a-\bar{v})O_2$ has a relatively small effect on estimating exercise cardiac output at the *AT*, particularly in patients with low *AT* values.

Oxygen Pulse and Stroke Volume

The O_2 pulse is calculated by dividing the $\dot{V}O_2$ by the simultaneously measured heart rate. It is the volume of O_2 taken up by the pulmonary blood during the period of a heartbeat and depends on the volume of O_2 extracted by the peripheral tissues. This measurement is useful

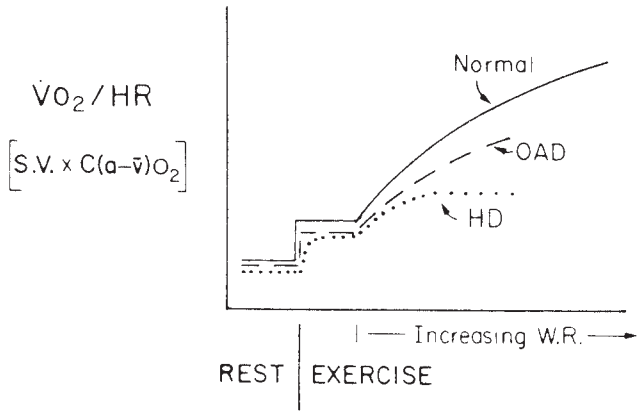

FIGURE 4.8. Characteristic changes in $\dot{V}O_2$/heart rate (HR) or stroke volume times $C(a-\bar{v})O_2$ (O_2 pulse) as related to increase in work rate (WR). Thus, patients with low stroke volumes, such as those with heart disease (HD), will tend to have low O_2 pulse values at maximal exercise. In contrast, patients with obstructive airway disease (OAD) have a pattern similar to that in normal subjects, although the values are lower at each work rate, reflecting the relatively low stroke volume in these patients.

because it equals the product of stroke volume and the arterial–mixed venous O_2 difference $[C(a-\bar{v})O_2]$. The immediate increase in O_2 pulse at the start of exercise depends primarily on the increase in stroke volume. As the work rate is increased, the O_2 pulse increases (Fig. 4.8), primarily because of an increasing $C(a-\bar{v})O_2$. If the stroke volume is reduced, the $C(a-\bar{v})O_2$ and, therefore, the O_2 pulse reach maximal values at a relatively low work rate. In this situation, the O_2 pulse has a low asymptote (see the heart disease curve in Fig. 4.8).[52] The O_2 pulse is also low in subjects with anemia, high levels of carboxyhemoglobin, marked arterial hypoxemia, and muscle mitochondrial or glycolytic enzyme defects, because of a reduced $C(a-\bar{v})O_2$ at maximal exercise.

Stroke volume is estimated from the O_2 pulse by the following equation:

$$SV = (O_2 \text{ pulse}/C(a-\bar{v})O_2) \times 100$$

where stroke volume is in milliliters per beat. The $C(a-\bar{v})O_2$ could be derived from Table 4.6 according to the hemoglobin concentration, modified by the factor noted in the footnotes of the table.

The O_2 pulse measured breath by breath in the transition from rest to exercise and from exercise to recovery is informative. The increase in O_2 pulse at the start of exercise depends on the size of the stroke volume increase and the increase in $C(a-\bar{v})O_2$. It will be low in patients who cannot increase their stroke volume in response to exercise.

Whereas the O_2 pulse promptly decreases in the normal subject when stopping exercise, as expected, it often transiently increases in patients with left ventricular failure (LVF) and exercise-induced myocardial ischemia. The explanation for this paradoxical response is that the afterload of the left ventricle is abruptly decreased when stopping exercise because of the immediate decrease in systemic arterial blood pressure. This allows improved ventricular ejection and increased stroke volume as the patient with the failing heart stops exercising.[40] The increase in stroke volume allows capillary blood flow to move more rapidly through the lung during the period of a heartbeat, thereby absorbing more O_2.

Anaerobic (Lactic Acidosis) Threshold

The *AT* is defined as the level of exercise $\dot{V}O_2$ above which aerobic energy production is supplemented by anaerobic mechanisms and is reflected by an increase in lactate and lactate-to-pyruvate (L/P) ratio in muscle[38] and arterial blood (see Figs. 2.12 and 2.13). The biochemical and physiological foundations of the *AT* hypothesis and their relationship to lactate increase and the development of lactic acidosis are diagrammed in Figure 4.9 and described experimentally in Chapter 2. The underlying mechanism for the *AT* measurement depends on the onset of anaerobic glycolysis leading to a net increase in lactic acid production (see Pathway B of Fig. 2.1). At work rates below the *AT*, the muscle[16,65] and blood[91] L/P

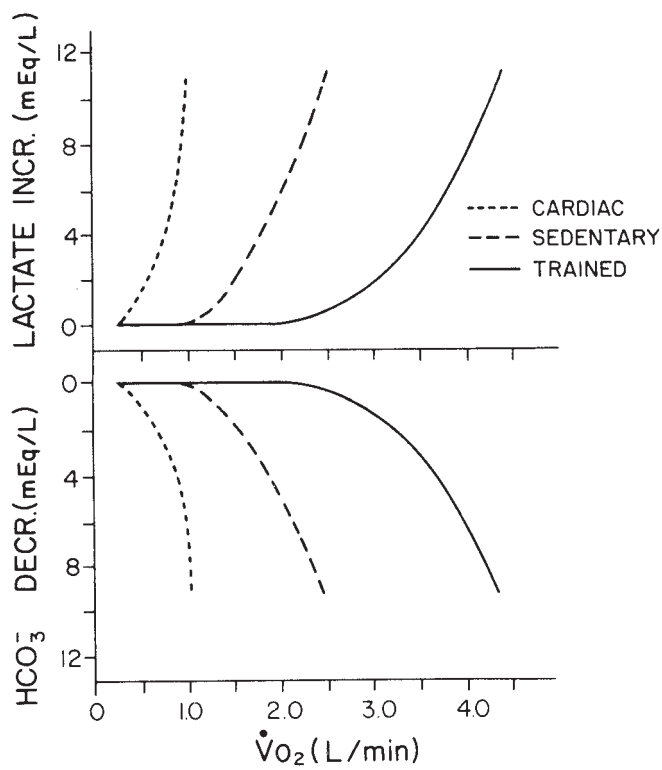

FIGURE 4.9. Lactate increase and bicarbonate decrease during incremental exercise in trained and sedentary normal subjects and in patients with primary cardiac disease of class II to III severity as defined by the New York Heart Association Classification. (Modified from Wasserman K, Whipp BJ. Exercise physiology in health and disease [state of the art]. *Am Rev Respir Dis.* 1975;112:219–249.)

ratio is the same as at rest, and no metabolic acidosis develops. Above the *AT*, a lactic acidosis develops. Thus, the threshold can be defined physiologically as the $\dot{V}O_2$ above which the critical capillary P_{O_2} has been reached and production of ATP through anaerobic glycolysis supplements the aerobic ATP production. It can also be defined in terms of changing redox state within the cell, as the $\dot{V}O_2$ at which lactate and L/P ratio increase (*LT*); or in terms of acid–base balance change, as the $\dot{V}O_2$ at which lactic acidosis develops (lactic acidosis threshold [*LAT*]). Like the $\dot{V}O_2$max, the threshold measurement is influenced by the size of the muscle groups involved in the activity.

Major Physiological Effects

In Chapter 2, the significance of the *AT* and the major changes that take place during the performance of exercise above as compared to below the *AT* were discussed. These include the development of metabolic acidosis with a sustained increase in blood lactate and L/P ratio. Plasma bicarbonate decreases inversely to the lactate increase, at a $\dot{V}O_2$ that depends on the level of fitness and wellness for aerobic work, as shown in Figure 4.9.

The *AT* also demarcates the exercise $\dot{V}O_2$ above which $\dot{V}O_2$ kinetics slow and above which exercise can no longer be performed in a true steady state (i.e., without anaerobic supplementation of ATP). Above the *AT*, ventilatory drive is stimulated by the metabolic acidosis resulting from lactate accumulation. Importantly, endurance time in the performance of a specific work task is reduced above the *AT* in proportion to the increase in lactate evoked by the exercise (see Fig. 2.11). The higher the lactate concentration, the shorter the endurance time and the steeper the rate of increase of $\dot{V}O_2$ during phase III of constant work rate exercise.[63] Other changes in physiological responses to exercise above the *AT* are described in Table 2.2.

Methods of Measurement

H^+ production is increased when lactate concentration is elevated in the cell. At the pH of cell water, virtually all of the increase in H^+ production must be buffered. The H^+ produced with the first 0.5 mmol per L increase in lactate appears to be buffered by newly generated HCO_3^- resulting from the alkaline reaction accompanying hydrolysis of PCr in muscle during early exercise (Figs. 2.25 and 2.26).[12,76,93] Above this initial increase in lactate, HCO_3^- buffers the newly produced H^+ stoichiometrically.[12,57,76] Thus, at work rates above the threshold, an obligatory increase in CO_2 production is produced above that from aerobic metabolism. It is equivalent to the CO_2 generated from the dissociation of HCO_3^- buffering of lactic acid, which is equal to the new lactate accumulating during exercise. It is relatively easy to detect the development of cellular lactic acidosis by measuring the rate of increase in $\dot{V}CO_2$ relative to that of $\dot{V}O_2$ during a progressively increasing exercise test. Beaver et al.[11] used a statistical regression method. Sue et al.[80] simplified the method, observing that the $\dot{V}CO_2$ versus $\dot{V}O_2$ relationship below the threshold had a slope consistently at or slightly less than 1.0, and that the slope changed to a value greater than 1.0 above the *AT*.

A relatively short, progressive work-rate test can rapidly determine the $\dot{V}O_2$ at which lactic acidosis develops when gas exchange is measured breath by breath or as the average of several breaths. The reason gas exchange is so effective in detecting the development of cellular metabolic acidosis is that the time delay between the HCO_3^- buffering of lactic acid in the cell and its appearance in the lung gas is only a matter of a few seconds. A flow diagram describing the sequence of gas exchange and ventilation changes in response to developing lactic acidosis for a progressively increasing work rate exercise test is shown in Figure 4.10. The changes in gas exchange that take place above the *AT* are illustrated in Figure 4.11.

V-Slope Method

When the net increase in lactate accumulation produces an acidosis, $\dot{V}CO_2$ accelerates relative to $\dot{V}O_2$. When these variables are plotted against each other, the relationship is composed of two apparently linear components, the lower of which (S_1) has a slope of slightly less than 1.0, whereas the upper component (S_2) has a slope steeper than 1.0 (see Fig. 2.32). The intercept of these two slopes is the *AT* as measured by gas exchange (see Fig. 4.11, lower left panel). The buffering of lactic acid causes an obligatory increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$ from the CO_2 produced when HCO_3^- buffers lactic acid. This technique is referred to as the *V-slope method* because it relates the increase in volume of CO_2 output to volume of O_2 uptake.

As shown in Figure 2.32, S_1 and S_2 can be determined from statistically derived regression slopes of $\dot{V}CO_2$ versus $\dot{V}O_2$ in the respective regions of interest. The break point or intercept of the two slopes can be selected by a computer program that defines the $\dot{V}O_2$ above which $\dot{V}CO_2$ increases faster than $\dot{V}O_2$, without hyperventilation. Sue et al.[80] pointed out that because S_1 must have a slope value of 1.0 or slightly less and S_2 a slope value of greater than 1.0 using the V-slope method, the break point representing the *AT* can be determined by placing a 45-degree right triangle on the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot (plotted on equal scales). The $\dot{V}O_2$ at which the data points start to increase at an angle greater than 45 degrees (slope > 1.0) is the *AT*. The values obtained by this method agree closely with the lactate threshold (*LT*) and, more precisely, the [HCO_3^-] threshold.[11,80] If a patient develops a lactic acidosis with only minimal exercise, the $\dot{V}CO_2$–$\dot{V}O_2$ plot may become steeper than 1.0 immediately after the start of unloaded exercise, and therefore the *AT* will be less than the lowest measured exercise $\dot{V}O_2$.

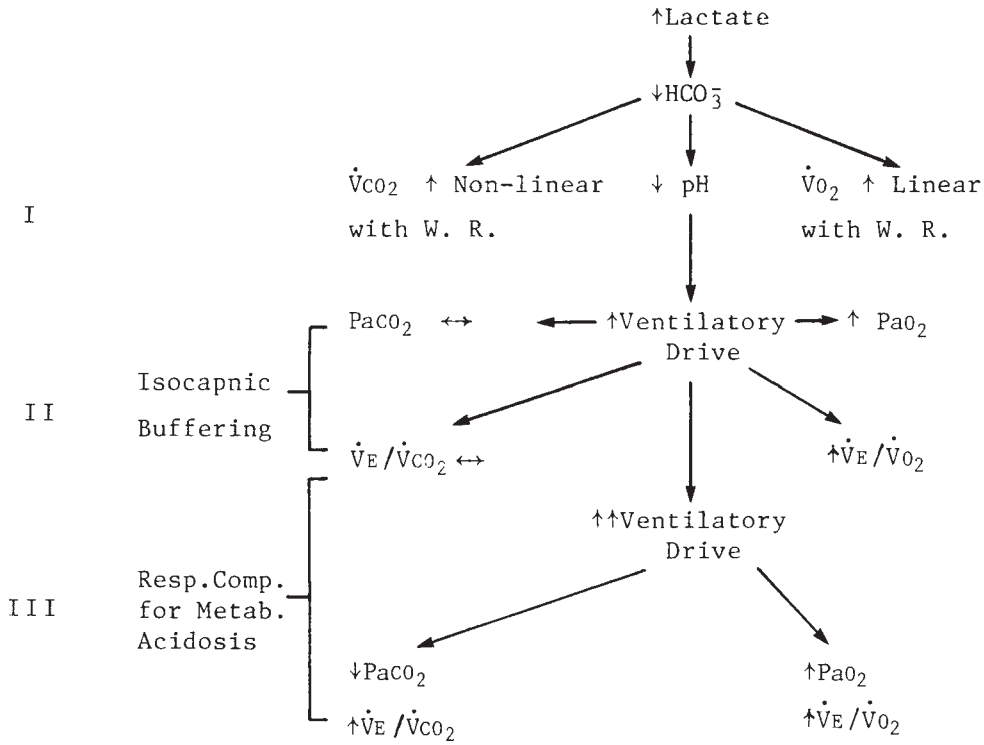

FIGURE 4.10. Diagram of effect of increasing lactate on gas exchange during a progressively increasing work rate exercise test. Small arrows directed upward indicate increases, small arrows directed downward indicate decreases, and horizontal arrows indicate no change. Mechanism I describes gas exchange that results solely from buffering of newly formed lactic acid (see lower left panel of Fig. 4.11). Mechanism II describes changes in arterial and end-tidal P_{CO_2} and P_{O_2} and ventilatory equivalents for O_2 and CO_2 that result from increased ventilatory drive consequent to CO_2 generated by buffering reaction (see right upper and lower panels of Fig. 4.11). Mechanism III describes changes caused by further increase in ventilatory drive consequent to respiratory compensation for metabolic acidosis (see changes to the right of *AT* lines in right upper and lower panels of Fig. 4.11).

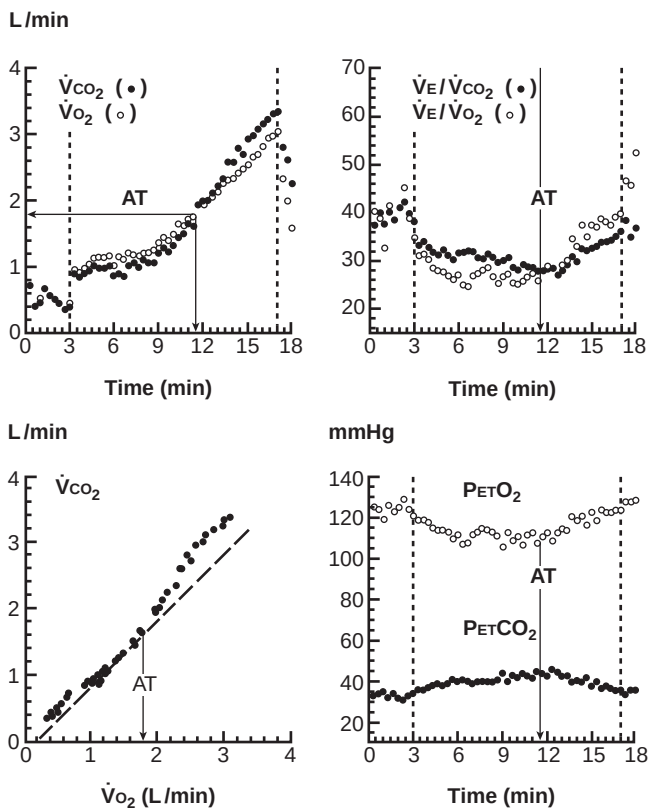

FIGURE 4.11. Gas exchange for a normal subject during a progressively increasing work rate exercise test to illustrate the gas exchange changes that take place at the anaerobic threshold (*AT*). The far-left vertical dashed line, in the three panels with time as the *x*-axis, indicates the start of unloading cycling. After 3 minutes of unloaded cycling, the work rate was increased 25 W/minute. The right vertical dashed line indicates the end of exercise. The V-slope plot of $\dot{V}CO_2$ versus $\dot{V}O_2$ is shown in the lower left panel. The diagonal line is at 45 degrees, or a slope of 1. The *AT* is where the $\dot{V}CO_2$ starts to increase faster than $\dot{V}O_2$, so the slope of the plot becomes steeper than 1. This is shown as the vertical arrow marked *AT*. The *AT* can also be located where the $\dot{V}E/\dot{V}O_2$ curve (**right upper panel**) inflects upward (*vertical dashed arrow labeled AT*). The nadir of the $\dot{V}E/\dot{V}O_2$ curve occurs at a higher work rate and reflects the start of ventilatory compensation for the metabolic acidosis. Because of the hyperventilation with respect to O_2, $P_{ET}O_2$ increases at the *AT* (**right lower panel**), whereas $P_{ET}CO_2$ does not start to decrease systematically until approximately 2 minutes later, coinciding with the increased ventilatory drive that serves to partially compensate for the decrease in arterial pH.

Although this method uses simultaneous measurements of $\dot{V}CO_2$ and $\dot{V}O_2$, it is independent of the subject's ventilatory response and insensitive to irregularities in breathing. Thus, it is useful for measuring the *AT* even in patients who do not develop ventilatory compensation for the exercise lactic acidosis, such as in patients with obesity syndrome or severe COPD. Despite its independence of the ventilatory response to exercise, some investigators erroneously refer to the V-slope method as the "ventilatory threshold." This is clearly wrong, because $\dot{V}E$ is an equal factor on both the *x*- and *y*-axes and therefore cannot account for the break point in the V-slope plot. The V-slope plot is actually a plot of moles of CO_2 output to moles of O_2 uptake. It is also the same as a plot of cardiac output × $C(\bar{v} - a)CO_2$ versus cardiac output × $C(a - \bar{v})O_2$. Therefore, the threshold is due to an increase in $C(\bar{v} - a)CO_2$ relative to $C(a - \bar{v})O_2$ as a result of the addition of CO_2 to the venous blood, as shown in Figures 2.21 and 2.32.

Ventilatory Equivalent Method

As the work rate is increased in a progressive exercise test (ramp or 1-minute steps), the linear pattern of increase in $\dot{V}CO_2$ and $\dot{V}E$ seen at low work rates (see Fig. 2.30) changes to a curvilinear pattern at high work rates, while $\dot{V}O_2$ continues to increase relatively linearly. $\dot{V}E$ and $\dot{V}CO_2$ initially accelerate equally above the *AT*. Therefore, $\dot{V}E/\dot{V}O_2$ and $PETO_2$ increase, whereas $\dot{V}E/\dot{V}CO_2$ and $PETCO_2$ remain constant for a brief period (isocapnic buffering; see Figs. 2.30 and 4.11). Thus, hyperventilation occurs with respect to O_2 but not CO_2 as the *AT* is exceeded. The isocapnic buffering period normally lasts about 2 minutes during incremental exercise tests. It is referred to as the isocapnic buffering period because ventilatory compensation for the developing metabolic acidosis had not yet started, although ventilation is responding to the excess CO_2 generated from HCO_3^- buffering.[89]

The increase in $\dot{V}E/\dot{V}O_2$ without an increase in $\dot{V}E/\dot{V}CO_2$ can only be caused by HCO_3^- buffering metabolic acid. It cannot be caused by other factors that increase ventilation out of proportion to $\dot{V}O_2$ (e.g., hypoxemia, pain, or psychogenic hyperventilation) because these would cause $\dot{V}E/\dot{V}CO_2$ to increase as well as $\dot{V}E/\dot{V}O_2$. When $\dot{V}E/\dot{V}O_2$ increases without a simultaneous increase in $\dot{V}E/\dot{V}CO_2$ during a progressively increasing work-rate test, it is a specific gas exchange demonstration that the *AT* has been surpassed (see Figs. 4.10 and 4.11).

One reason for increasing work rate relatively rapidly during the progressively increasing work-rate test is to take advantage of the finding that the CO_2 contribution from buffering is observed only during the buffering process (the period of decreasing bicarbonate) and not after the lactate has been buffered. Thus, CO_2 generated from buffering is evident in the expired gas only when lactate and HCO_3^- are changing, but not after they have already changed. Increasing the work rate at a relatively fast rate will result in a higher rate of lactate accumulation and steeper S_2 above the *AT* than when the rate of increase in work rate is relatively slow.[19]

As the work rate is increased further above the *AT*, the carotid bodies respond to the decreasing pH and ventilatory stimulation is intensified (see Fig. 4.10, mechanism III; also Figs. 2.30 and 4.11). This causes $PaCO_2$ to decrease, preventing pH from falling as much as would be predicted by the addition of lactic acid to a closed system. This ventilatory compensation for the lactic acidosis is reflected in an increase in $\dot{V}E/\dot{V}CO_2$ and a decrease in $PaCO_2$ and $PETCO_2$, as well as by further increases in $\dot{V}E/\dot{V}O_2$ and $PETO_2$ (see Figs. 2.30 and 4.11). When ventilatory compensation for metabolic acidosis starts, the $\dot{V}O_2$ is well above the *AT*, *LT*, or *LAT*. This $\dot{V}O_2$ is referred to as the *ventilatory compensation point* (VCP). The *AT* is measured as metabolic stress—that is, in units of O_2 uptake, not work rate. In contrast to the VCP, the *AT* is unaffected by the rate at which the work rate is incremented[14,21] or by metabolic substrate.[19,47,113]

Improving Estimation of the Anaerobic Threshold

Occasionally, the *AT* cannot be reliably detected by the ventilatory equivalent method (see Fig. 4.10, mechanism II) because of irregular breathing, an inappropriate rate of increase in work rate, suboptimal plotting scales, or a poor ventilatory response by the patient to the metabolic acidosis. To obviate these problems, one can measure blood lactate or standard bicarbonate directly. Beaver et al.[10] found that the *LT* during exercise can be most reliably selected by plotting log arterial blood lactate against log $\dot{V}O_2$. Similarly, the start of the arterial $[HCO_3^-]$ fall, indicating the start of developing lactic acidosis (*LAT*), can be most reliably detected from a plot of log standard arterial $[HCO_3^-]$ against log $\dot{V}O_2$.[12] A slight difference exists in the $\dot{V}O_2$ for these thresholds. *LT* precedes *LAT* because of non-HCO_3^- buffering of the initial lactic acid increase.[76] Although we distinguish between *LT* and *LAT* for scientific correctness, the distinction is not of clinical significance.

When the break point between S_1 and S_2 is not clear using the V-slope method, it is likely that the rate of CO_2 released from HCO_3^- buffering of lactic acid is slow because the rate of increase in work rate is slow relative to the subject's fitness during the progressively increasing work-rate test.[90] Alternatively, the patient may not produce lactic acid, such as in muscle phosphorylase deficiency (McArdle syndrome).[61] In the former instance, the test should be repeated with a faster rate of increase in work rate. If the break point ($\dot{V}CO_2$ increasing faster than $\dot{V}O_2$) is still not observed, the possibility should be investigated that the patient is unable to raise blood lactate levels because of a muscle metabolic defect.

Heart Rate–Oxygen Uptake Relationship and Heart Rate Reserve

Heart rate normally increases linearly with $\dot{V}O_2$ during increasing work rate exercise (Fig. 4.12).[24] In heart diseases unrelated to conduction defects, the heart rate often increases relatively steeply for the increase in $\dot{V}O_2$ because the stroke volume is reduced. In addition, $\dot{V}O_2$ commonly slows its rate of increase with work rate when the myocardium becomes ischemic, as in patients with coronary artery disease. Because heart rate typically continues to increase in patients whose heart rates are not slowed by β-adrenergic blockade, the rate of increase in heart rate relative to $\dot{V}O_2$ becomes steeper, deviating from the linearity established at lower work rates (see Fig. 4.12). This implies that stroke volume is decreasing and that cardiac output may not be increasing in pace with the O_2 requirement. Although this curvilinear increase in the heart rate–$\dot{V}O_2$ relationship is not uniformly seen in patients with heart disease, it is a useful diagnostic observation and suggests a significant worsening in left ventricular function with increasing work rate.[42] Pulmonary vascular disease is also associated with a steep heart rate response because venous return to the left side of the heart and therefore left ventricular output are low in this disorder.

Patients with airflow obstruction (see Fig. 4.12) commonly have a moderately elevated heart rate response at a given $\dot{V}O_2$ due to a reduced stroke volume. The latter results from a restriction in cardiac filling[15] due to high intrathoracic pressure during exhalation, or to encroachment of the lung on the cardiac fossa, or both. Heart rate increases linearly with $\dot{V}O_2$ in this disorder. However, the maximum heart rate in the patient with ventilatory limitation is usually below the predicted value because the patient becomes ventilatory limited before the cardiovascular system is maximally stressed.[52]

The estimated *heart rate reserve* is a measure of the difference between the predicted maximal heart rate, based on age, and the measured heart rate at peak $\dot{V}O_2$. (See the section on maximal heart rate and heart rate reserve in Chapter 7 for normal values.) Although the predicted maximal heart rate has considerable variation, as determined from population studies, the heart rate reserve is still a useful concept for differential diagnosis. Table 4.7 lists disorders in which the heart rate reserve may be increased. Normally, the heart rate reserve is relatively small (less than 15 bpm). It is also usually normal in patients with silent myocardial ischemia and valvular heart disease and in patients with disorders of the pulmonary circulation. In contrast, patients with peripheral arterial disease and patients with COPD become symptom-limited before the predicted maximal heart rate is reached. Patients with disorders of the conducting system of the heart, or sinoatrial node, may also have a low maximum heart rate. Patients who take β-adrenergic blocking drugs or patients who are limited in exercise because of heart block or sick sinus syndrome have a large heart rate reserve. Finally, those patients who make a poor effort have an increased heart rate reserve because they fail to maximally stress their cardiovascular system at the time they stop exercising.

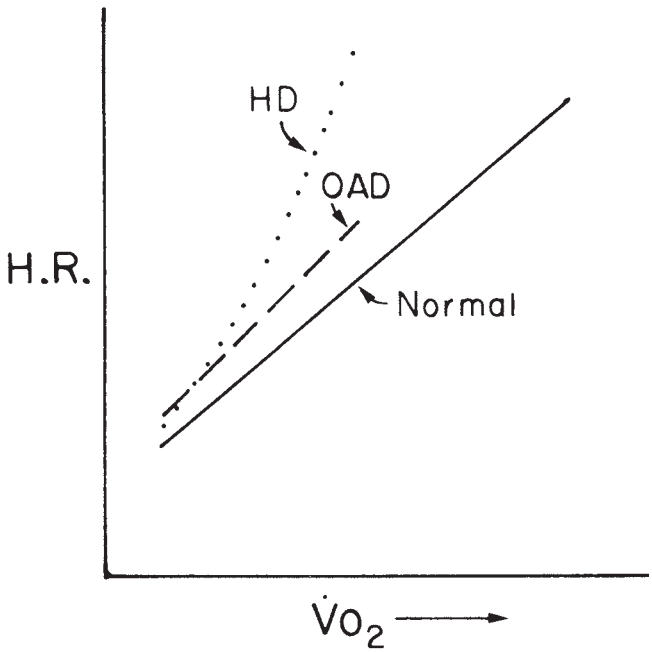

FIGURE 4.12. Characteristic changes in heart rate (HR) relative to $\dot{V}O_2$ for normal subjects, for patients with chronic obstructive airway disease (OAD), and for those with heart disease (HD) without chronotropic incompetence. The steeper heart rate–$\dot{V}O_2$ relationship for the patient with obstructive airway disease may reflect relative unfitness or reduced stroke volume secondary to disturbed lung mechanics or pulmonary vascular occlusion. In contrast, the relatively low maximum heart rate reflects respiratory limitation to the maximum level of exercise. The steepening heart rate– $\dot{V}O_2$ relationship seen in some patients with heart disease reflects the failure of $\dot{V}O_2$ to increase, normally, in response to the increasing work rate, as illustrated in Figure 4.5C.

Table 4.7

Disorders Associated with Increased Heart Rate Reserve

Claudication limiting exercise
Angina limiting exercise
"Sick sinus" syndrome
β-Adrenergic blockade
Lung disease with impaired ventilatory mechanics
Poor effort

Arterial Blood Pressure

Arterial pressure measurements, particularly when directly measured, are helpful for diagnostics as well as for patient safety. The normal responses of systolic, diastolic, and pulse pressures are described in Chapter 7 (in the section "Brachial Artery Blood Pressure"). Normally, the systolic pressure increases to a much greater degree than the diastolic pressure and in proportion to the work rate increase. A decrease in systolic and pulse pressures with increasing work rate suggests important cardiac dysfunction and indicates that the exercise test should stop. The direct arterial pressure tracing (made at a fast recorder speed) showing a slow rise in arterial pressure may provide evidence for ventricular outflow obstruction, such as seen with aortic stenosis or hypertrophic cardiomyopathy.

Breathing Reserve

The breathing reserve is expressed as either the difference between the maximal voluntary ventilation (MVV) and the maximum exercise ventilation in absolute terms or this difference as a fraction of the MVV (Table 4.2 and Fig. 4.13). Except in extremely fit individuals who can attain exceptionally high metabolic rates, normal males have a breathing reserve of at least 11 L per minute, or 10% to 40% of the MVV (Fig. 4.14).[78] Female athletes might also have a low breathing reserve during exercise because, relative to height, females have a lower MVV than males. A low breathing reserve is characteristic of patients with primary lung disease who have ventilatory limitation. The breathing reserve is high when cardiovascular or other diseases limit exercise performance.

Expiratory Flow Pattern

The expiratory flow pattern can be useful in detecting airway obstruction during exercise. The peak expiratory flow rate is near the middle of the expiratory phase of respiration in normal subjects and has an appearance of a half sine wave. In contrast, the expiratory flow pattern of the patient with obstructive airway disease has an early peak and appears trapezoidal because exhalation effort is sustained with an abrupt termination of expiration, when the next inspiration is initiated (Fig. 4.15). This pattern can acutely normalize in asthmatic patients after the use of inhaled bronchodilators (see Fig. 4.15). Although the expiratory flow pattern gives only qualitative evidence of airflow obstruction during exercise, it is obtained simply by recording expired airflow, breath by breath. Flow–volume analysis[7,27] can give similar information to that of the flow–time analysis.

Inspiratory Capacity

It has long been recognized that functional residual capacity (FRC) increases in many patients with COPDs.[6] O'Donnell et al.[53] emphasized the value of the reduction in inspiratory capacity (IC) during exercise consequent to the development of hyperinflation and increase in FRC during exercise in patients with COPD. In normal subjects, the IC is maintained or slightly increases during exercise,[107] reflecting a decrease in FRC. In contrast, the IC decreases during exercise in COPD, reflecting hyperinflation and air trapping as the respiratory rate increases. This reduction in IC in COPD has been used to assess severity of disease. The increase in IC has been used to evaluate the therapeutic efficacy of O_2 breathing[73] and bronchodilators[53] in COPD.

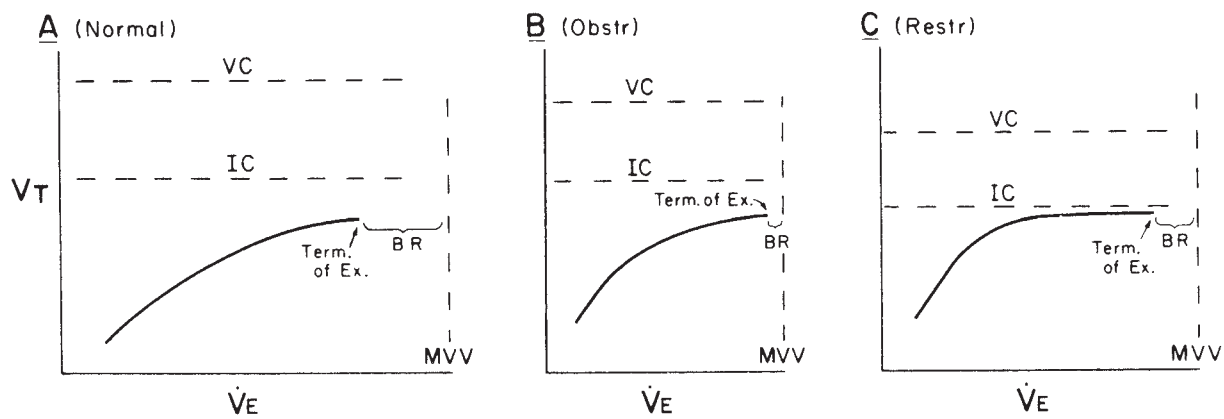

FIGURE 4.13. Examples of tidal volume change as related to minute ventilation during incremental exercise testing in a normal subject **(A)** and in patients with obstructive **(B)** and restrictive **(C)** lung diseases. The curve ends at the subject's maximal exercise ventilation. The vertical dashed line indicates the subject's maximum voluntary ventilation (MVV). The horizontal dashed lines show the vital capacity (VC) and inspiratory capacity (IC) on the *y*-axis. The distance between the highest $\dot{V}_E$ and MVV on the *x*-axis is the subject's breathing reserve (BR). In the case of patients with obstructive lung disease, the BR is quite small. In restrictive lung diseases, the IC is reduced and V_T closely approximates the IC near and at peak exercise.

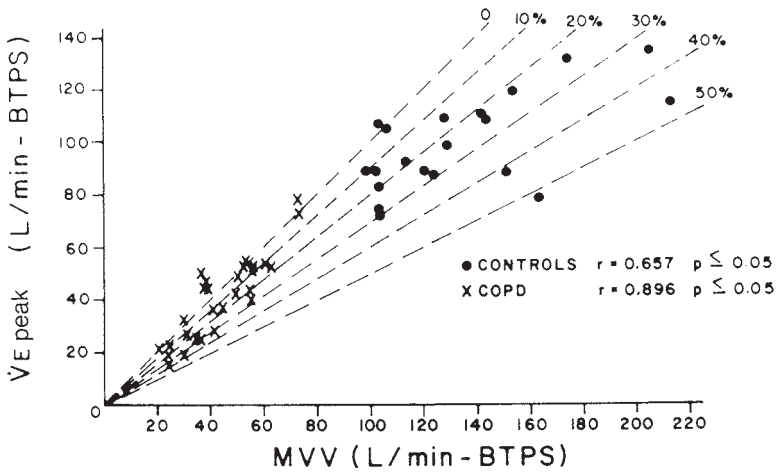

FIGURE 4.14. Maximum exercise ventilation ($\dot{V}_E$ peak) as related to maximum voluntary ventilation (MVV) in patients with chronic obstructive pulmonary disease (COPD) and in normal subjects. The dashed-line isopleths indicate the percentage of breathing reserve [(MVV – $\dot{V}_E$ peak)/MVV] × 100. The *r* values are the correlation coefficients for the control and the COPD groups.

Tests of Uneven $\dot{V}_A/\dot{Q}$

Wasted Ventilation and Dead Space/Tidal Volume Ratio

Alveolar ventilation ($\dot{V}_A$) is the theoretical ventilation participating in pulmonary gas exchange if the ventilation–perfusion ratios of all alveolar units were the same. This is the "ideal" lung. It is the lowest alveolar ventilation for a given $\dot{V}CO_2$. In the ideal lung, the mean alveolar PCO_2 is assumed to equal the arterial PCO_2. However, the lung usually does not have ideal properties, and the actual minute ventilation includes ventilation to non–gas-exchange conducting airways and alveoli that may not be ideally perfused. The difference between the actual minute ventilation and the ideal alveolar ventilation is the physiological dead space ventilation (which includes the anatomical dead space). A valuable estimate of the degree of mismatching of ventilation to perfusion during exercise is the physiological dead space/tidal volume ratio (V_D/V_T). The V_D/V_T is lowest when alveolar ventilation relative to perfusion is uniform.

At rest, the physiological dead space volume is normally about one-third of the tidal volume. During exercise, it is reduced to about one-fifth of the tidal volume,[95] with the major decrement occurring at the lowest work rates. In patients with airway disorders, ventilation–perfusion relationships are uneven primarily because of nonuniform ventilation. In patients with pulmonary vascular disease, ventilation–perfusion relationships are uneven primarily because of nonuniform perfusion of ventilated lung. In both disorders, V_D/V_T is higher, particularly during exercise, because the V_D/V_T is increased at rest and fails to decrease during exercise.

The V_D/V_T is a valuable measurement because it is typically abnormal in patients with primary pulmonary vascular disease or pulmonary vascular disease secondary to obstructive or interstitial lung disease and patients with heart failure. This is discussed in greater detail in Chapter 5. An elevated V_D/V_T is sometimes the only gas-exchange abnormality evident during exercise testing.[42] Figure 4.16 illustrates the pattern of change in V_D/V_T as the work rate is increased in the normal individual and in patients with nonuniform alveolar ventilation–perfusion ratios ($\dot{V}_A/\dot{Q}$) resulting from lung or pulmonary vascular diseases. In patients with nonuniform $\dot{V}_A/\dot{Q}$, the V_D/V_T

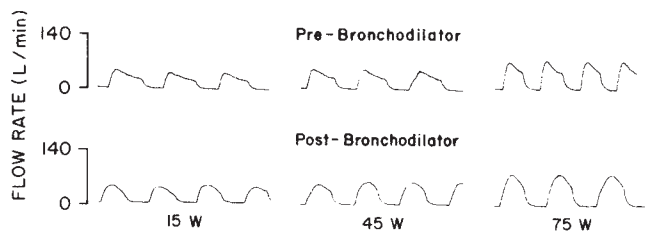

FIGURE 4.15. Expiratory flow pattern in an asthmatic subject at increasing work rates before and after acute bronchodilator therapy. (From Brown HV, Wasserman K, Whipp BJ. Strategies of exercise testing in chronic lung disease. *Bull Eur Physiopathol Resp.* 1977;13:409–423, with permission.)

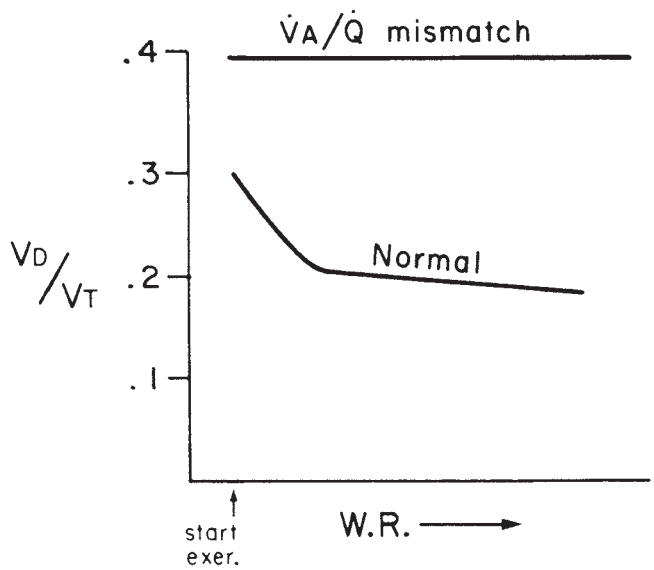

FIGURE 4.16. Example of the change in the ratio of physiologic dead space to tidal volume (V_D/V_T) during rest and at increasing work rate (WR) for a normal subject and a patient with ventilation–perfusion ($\dot{V}_A/\dot{Q}$) mismatch.

may be only slightly elevated at rest, but it remains relatively unchanged during exercise or even increases if a right-to-left shunt develops during exercise (opening a foramen ovale). Thus, exercise brings out the abnormality in ventilation–perfusion relationships.

When V_D/V_T is increased, $\dot{V}_E$ is typically inordinately high for the work rate performed. $\dot{V}_E$ may also be high in conditions in which the P_aCO_2 is relatively low (low CO_2 set point), such as with a chronic metabolic acidosis. In this setting, V_D/V_T will be normal if the lungs are normal, and arterial blood gas analysis will reveal a low P_aCO_2 (hyperventilation). Therefore, a high $\dot{V}_E$ at a given work rate (high $\dot{V}_E/\dot{V}CO_2$) is indicative of either high V_D/V_T or hyperventilation. The two pathophysiologic mechanisms can be differentiated by measuring gas exchange and arterial blood gases simultaneously.

Figure 4.17 shows the $\dot{V}_E$ required for various metabolic rates ($\dot{V}CO_2$) for designated values of P_aCO_2 and V_D/V_T. This plot is useful for demonstrating the relationships between $\dot{V}_E$, P_aCO_2, $\dot{V}CO_2$, and V_D/V_T. It also serves as a nomogram to determine V_D/V_T when the three other variables are known.

Arterial PO_2 and Alveolar–Arterial PO_2 Difference

Normally, P_aO_2 does not decrease during exercise, and the $P(A-a)O_2$ remains under 20 to 30 mm Hg (Fig. 4.18A).[31,95,109] In patients with airway disease, a reduced P_aO_2 and an increased $P(A-a)O_2$ during progressively increasing work rate exercise testing (see Fig. 4.18B) typically result from underventilation of regions of lung relative to their perfusion—that is, lung units with low alveolar ventilation-to-perfusion ratios.[87,95] During exercise, when cardiac output increases, causing more desaturated blood to flow through low-$\dot{V}A/\dot{Q}$ areas of the lungs, arterial hypoxemia becomes more marked. Fortunately, the blood vessels in the poorly ventilated low-$\dot{V}A/\dot{Q}$ areas of the lung normally constrict under the influence of decreasing alveolar P_O2.[26] This diversion of blood flow to areas of relatively good ventilation is a protective mechanism because it reduces the degree of hypoxemia that would otherwise occur. This mechanism prevents progressive hypoxemia as the work rate is increased in patients with COPD (see Fig. 4.18B).

Exercise hypoxemia may also develop in patients with pulmonary fibrosis or pulmonary vascular disease. Because all recruitable pulmonary blood vessels are functioning at rest in patients with a reduced pulmonary capillary bed, when cardiac output increases, no additional pulmonary capillaries are available to be recruited to accommodate the increase in pulmonary blood flow during exercise. Thus, the red cell transit must increase at rest and further increase during exercise (decrease in residence time), resulting in reduced time for diffusion equilibrium between alveolar O_2 and red cell O_2. This pattern of decreasing P_aO_2 and increasing $P(A-a)O_2$ with increasing work rate reflects a decrease in residence time of red cells

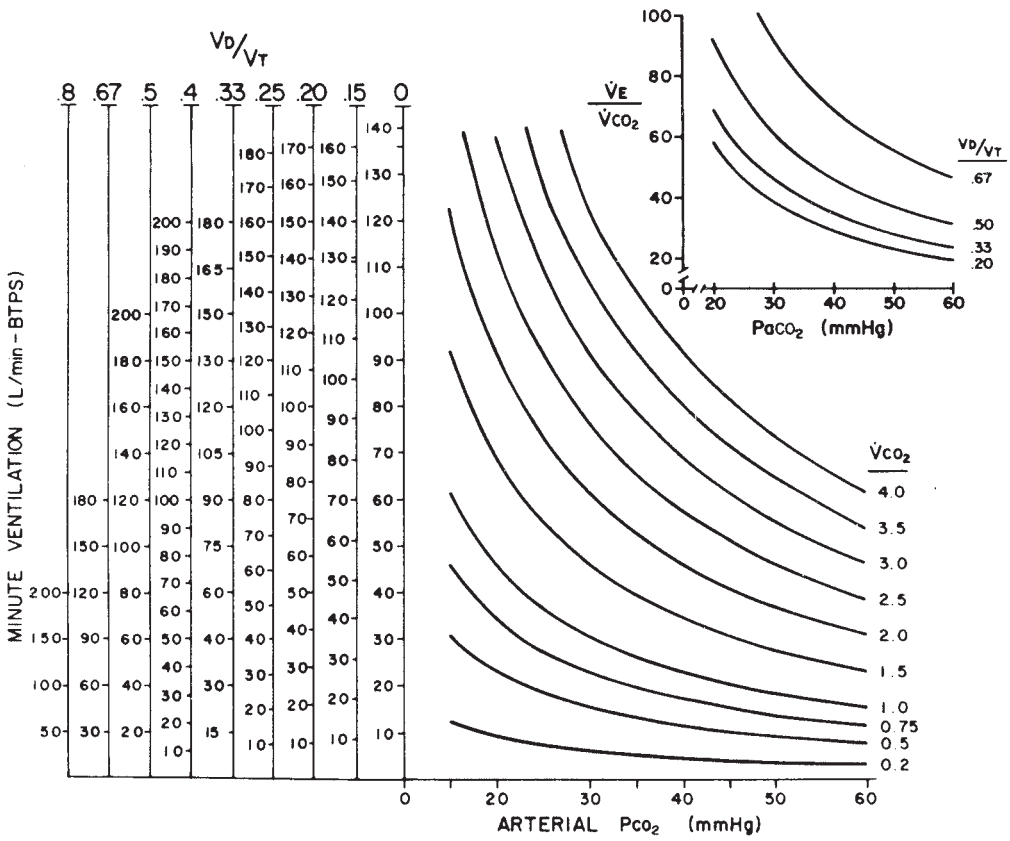

FIGURE 4.17. Minute ventilation ($\dot{V}_E$) required for various values of $\dot{V}CO_2$, as related to arterial P_{CO_2} (P_aCO_2) for various physiologic dead space/tidal volume (V_D/V_T) fractions (*y*-axes). If any three of the foregoing values are known, the fourth can be determined. For instance, if $\dot{V}_E$, $\dot{V}CO_2$, and P_aCO_2 are measured, then V_D/V_T can be determined from the ordinate that agrees with the measured $\dot{V}_E$. The inset shows the effect of changing P_aCO_2 on the $\dot{V}_E/\dot{V}CO_2$ ratio during exercise with a given V_D/V_T. (From Wasserman K, Whipp BJ. Exercise physiology in health and disease [state of the art]. *Am Rev Respir Dis.* 1975;112:219–249, with permission.)

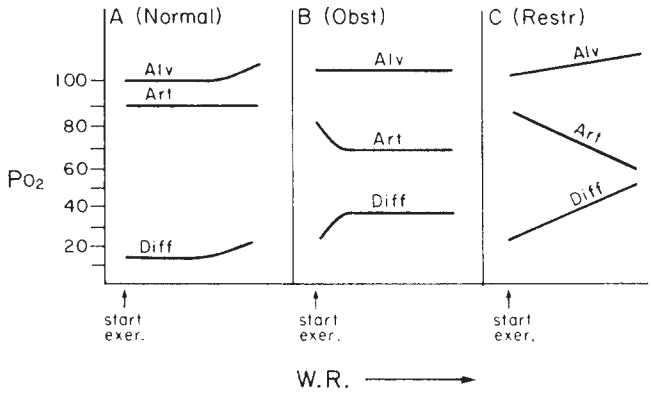

FIGURE 4.18. General pattern of arterial and alveolar P_{O_2} and alveolar-arterial P_{O_2} differences in normal subjects **(A)** and in patients with obstructive **(B)** and restrictive **(C)** lung diseases as related to increasing work rate (WR).

in the pulmonary capillaries when the pulmonary capillary blood volume is critically reduced. Consequently, disorders in which pulmonary capillary blood volume is reduced and accompanied by exercise-induced hypoxemia due to reduced time for diffusion equilibrium, hypoxemia becomes more pronounced as the work rate and pulmonary blood pressure and flow increase (see Fig. 4.18C).

Pa_{O_2} also decreases as the work rate is increased in conditions in which the alveoli are filled with material in which O_2 is relatively insoluble (e.g., as in pulmonary alveolar proteinosis). When the perfusion increases in these lung units, O_2 in the gas space fails to equilibrate with O_2 in the red cell (alveolar capillary block), and hypoxemia becomes more marked as the blood flow increases (a diffusion defect). At rest, however, when pulmonary blood flow is relatively low, Pa_{O_2} may be normal because red cell residence time in the pulmonary capillary is long enough (>0.3 second) to reach diffusion equilibrium.

Hypoxemia will worsen in patients with lung disease when a potentially patent foramen ovale opens as right atrial pressure exceeds left atrial pressure. This causes part of the venous return to shunt from right to left at the atrial level. A simple, sensitive test to diagnose a right-to-left shunt that develops during exercise uses 100% O_2 breathing. For example, when breathing 100% O_2, the Pa_{O_2} is reduced approximately 100 mm Hg below normal (600 mm Hg) for each 5% right-to-left shunt until the Pa_{O_2} reaches a low value of 150 mm Hg. The decrease in Pa_{O_2} is then smaller for a given shunt size.

Calculation of $P(A - a)_{O_2}$ may reveal abnormalities in blood oxygenation masked by hyperventilation. An abnormally elevated $P(A - a)_{O_2}$ is indicative of uneven $\dot{V}_A/\dot{Q}$, a diffusion defect, and/or a right-to-left shunt.

Arterial–End-Tidal P_{CO_2} Difference

Alveoli that are underperfused or unperfused have a low CO_2 concentration. The ventilation of these alveoli is wasted (alveolar dead space) because these alveoli cannot participate fully in gas exchange. Thus, the mixed expired and end-tidal P_{CO_2} values are reduced relative to the arterial P_{CO_2}. By measuring the arterial–end-tidal P_{CO_2} difference $[P(a - ET)CO_2]$, we have another measurement that can be used as evidence of increased alveolar dead space or uneven $\dot{V}_A/\dot{Q}$ (Fig. 4.19).[36,79,95]

In the healthy lung, Pa_{CO_2} is approximately 2 mm Hg greater than P_{ETCO_2} at rest. During exercise, however, P_{ETCO_2} increases relative to Pa_{CO_2} and normally exceeds it (see Fig. 4.19A and data in Chapter 7). The mechanism for this is relatively straightforward. Because of the increased rate of CO_2 delivery to the lung associated with the high rate of CO_2 production during exercise, alveolar P_{CO_2} continues to increase during exhalation. P_{ETCO_2} is the highest alveolar P_{CO_2} during the respiratory cycle, approaching the mixed venous value. On the other hand, the Pa_{CO_2} is determined by the alveolar P_{CO_2} during the entire respiratory cycle. Therefore, provided that the functioning alveoli are relatively uniformly perfused, the end-of-breath P_{CO_2} (P_{ETCO_2}) will exceed the average of the changing alveolar P_{CO_2} (Pa_{CO_2}) during the respiratory cycle.

Direct measurements of continuously measured P_{CO_2} in the expired air and Pa_{CO_2} are shown in Figure 4.20. The slope of instantaneously measured exhaled P_{CO_2} during the alveolar phase of the breath increases as work rate increases. Thus P_{ETCO_2} normally exceeds Pa_{CO_2} during exercise and $P(a - ET)CO_2$ is negative by about 4 mm Hg. The slower the breathing rate, the closer P_{ETCO_2} would be to mixed venous P_{CO_2}, making $P(a - ET)CO_2$ even more negative.

If the $P(a - ET)CO_2$ remains positive during exercise, this is evidence for decreased perfusion to ventilated alveoli (uneven $\dot{V}_A/\dot{Q}$ with high-$\dot{V}_A/\dot{Q}$ units) (see Fig. 4.19B, C). An extreme situation may be seen when CO_2-rich venous blood is diverted to the left side of the circulation without passing through the lungs during exercise (right-to-left shunt). In this case, Pa_{CO_2} is much higher

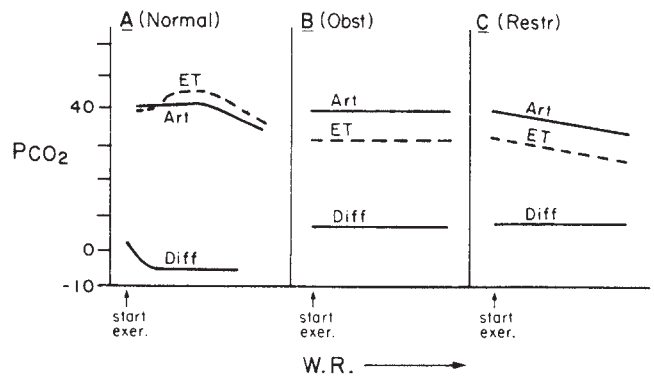

FIGURE 4.19. Pattern of change in arterial and end-tidal (ET) P_{CO_2} and arterial–end-tidal P_{CO_2} difference in normal subjects **(A)** and in patients with obstructive **(B)** and restrictive **(C)** lung diseases for increasing work rate exercise. All have normal resting Pa_{CO_2} values.

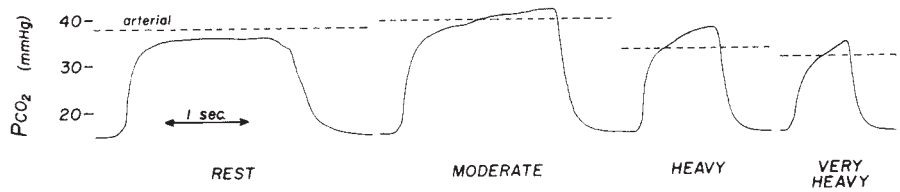

FIGURE 4.20. Arterial (*dashed lines*) compared to instantaneous airway (*solid lines*) P_{CO_2} for the resting state and increasing intensities of exercise in a normal subject. The end-tidal P_{CO_2} is less than P_{aCO_2} at rest but greater than P_{aCO_2} during exercise. (From Wasserman K, Van Kessel A, Burton GG. Interaction of physiological mechanisms during exercise. *J Appl Physiol.* 1967;22:71–85, with permission.)

than P_{ETCO_2} because the blood perfusing the lung is hyperventilated to compensate for the CO_2 load entering the arterial circulation through the shunt.[69,81] In this situation, $P(a-ET)CO_2$ is markedly positive because of a decreased P_{ETCO_2} during exercise. The magnitude of the increased $P(a-ET)CO_2$ depends on the size of the right-to-left shunt.

Sue et al.[79] compared the resting diffusing capacity of the lung for carbon monoxide (DLCO) with arterial blood gases during maximal exercise in 276 male shipyard workers. Fourteen of 16 subjects with DLCO less than 70% had abnormal gas exchange, measured as an increase in $P(A-a)O_2$, VD/VT, or $P(a-ET)CO_2$, during exercise. However, 88 subjects had abnormal exercise gas exchange with a normal DLCO. Increases in VD/VT and $P(a-ET)CO_2$ occurred when there was a major component of uneven, high-$\dot{V}A/\dot{Q}$ lung units. Both were abnormal in the same subjects. In contrast, an increase in $P(A-a)O_2$ was abnormal when there was a major component of uneven, low-$\dot{V}A/\dot{Q}$ lung units. An increased $P(a-ET)CO_2$ and VD/VT occurred more frequently than an increased $P(A-a)O_2$. When $P(A-a)O_2$ was increased, $P(a-ET)CO_2$ and VD/VT were also increased. In many instances, however, only $P(a-ET)CO_2$ and VD/VT were abnormal, without $P(A-a)O_2$ being abnormal.

Ventilatory Equivalents as Indices of Uneven $\dot{V}A/\dot{Q}$

As described previously, the measurements of VD/VT, $P(a-ET)CO_2$, and $P(A-a)O_2$ quantify the degree of $\dot{V}A/\dot{Q}$ mismatching and, thereby, inefficient gas exchange. To obtain these measurements, arterial blood gas sampling is required. Because the consequence of inefficient gas exchange dictates an increased ventilatory requirement to eliminate a given amount of CO_2 from the body, two noninvasive techniques have been used to measure $\dot{V}A/\dot{Q}$ mismatching: the slope of $\dot{V}E$ as a function of $\dot{V}CO_2$ in the range of exercise below the VCP,[17,37,48,50,82] and the nadir of the ventilatory equivalent for CO_2, which occurs at and between the *AT* and VCP, the values of which are essentially identical.[82] Normal values for the slope and ratio, adjusted for age and gender, are given in Chapter 7.

Figure 4.21 shows the difference between the slope and the ratio at and between *AT* and VCP in three normal subjects. Although the difference between these two measurements is small, the slope of $\dot{V}E$ versus $\dot{V}CO_2$, measured below the VCP, is usually slightly less than $\dot{V}E/\dot{V}CO_2$ at the *AT* or VCP, depending on the size of the positive intercept on the *y*-axis of the $\dot{V}E$ versus $\dot{V}CO_2$ plot.[82] A small positive intercept is generally present in normal subjects when $\dot{V}E$ is plotted against $\dot{V}CO_2$, starting from the lowest level of exercise. The intercept is positive if the VD/VT decreases as work rate increases and/or there is early hyperventilation that gradually dissipates as work rate increases (see subject 2, Fig. 4.21). In contrast, if the intercept of the $\dot{V}E$ versus $\dot{V}CO_2$ plot is at or near zero (no early hyperventilation and no large decrease in VD/VT), the slope of $\dot{V}E$ versus $\dot{V}CO_2$ below the VCP and the $\dot{V}E/\dot{V}CO_2$ in the range of the *AT* and VCP are approximately equal (subject 3, Fig. 4.21). Typically, there is a small positive intercept in most normal subjects below the VCP, making the slope a little less than the ratio of $\dot{V}E/\dot{V}CO_2$ at the *AT* and VCP (see subject 1, Fig. 4.21). However, the $\dot{V}E/\dot{V}CO_2$ slope commonly intercepts at zero in pulmonary vascular disease because these patients cannot decrease their VD/VT during exercise. Therefore, the slope and ratio would be similar in these patients.

Because the $\dot{V}E/\dot{V}CO_2$ ratio at the *AT* is less variable than the slope of $\dot{V}E$ versus $\dot{V}CO_2$ below the VCP,[82,88] we prefer the ratio of $\dot{V}E/\dot{V}CO_2$ in the range of the *AT* and VCP to the slope. No special calculation is required to obtain this ratio, in contrast to the regression slope through a selected range of values below the VCP as in the case of $\dot{V}E$ versus $\dot{V}CO_2$ (panel 6 of the nine-panel plot shown in figure 4.32 and the cases presented in chapter 10). The $\dot{V}E/\dot{V}CO_2$ is read directly from panel 4 of the nine-panel plot of exercise physiological data at the *AT* or VCP. It is the $\dot{V}E/\dot{V}CO_2$ value least affected by anxiety hyperventilation and the H^+ stimulus to the carotid bodies caused by the exercise lactic acidosis.

The range of normal values for the slope of $\dot{V}E$ versus $\dot{V}CO_2$ below the VCP and $\dot{V}E/\dot{V}CO_2$ at *AT*, as related to age and gender, is described in Chapter 7. The values are the same for cycle and treadmill exercise. Although small in most systems, the breathing valve dead space is variable

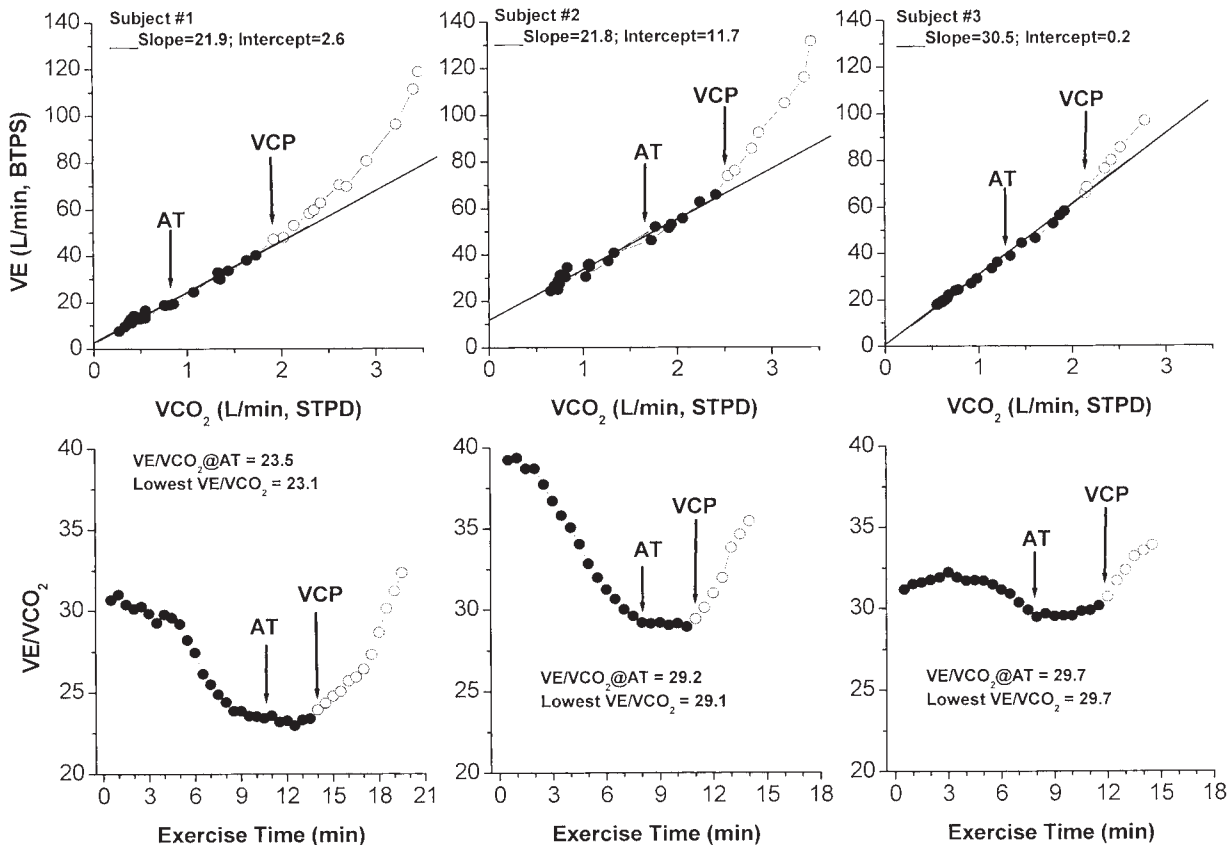

FIGURE 4.21. Comparison of $\dot{V}E$-versus-$\dot{V}CO_2$ slopes in three normal subjects (**upper panels**) and the $\dot{V}E/\dot{V}CO_2$ ratios as related to time in the same three studies (**lower panels**). Data points are shown every 0.5 minute during progressively increasing cycle ergometer exercise. The open symbols occur above the ventilatory compensation points (VCP) and are not used for calculation of the slopes (*straight solid lines*) and intercepts of VE versus $\dot{V}CO_2$. The $\dot{V}E/\dot{V}CO_2$ values (**lower panels**) reach a nearly constant nadir between the anaerobic threshold (*AT*) and VCP arrows. Subject 1 is typical of an average response, subject 2 has an unusually large positive intercept for $\dot{V}E$-versus-$\dot{V}CO_2$ slope, and subject 3 has an intercept close to zero. Although the $\dot{V}E$-versus-$\dot{V}CO_2$ slopes for subjects 1 and 2 are similar, their *y*-axis intercepts differ; thus, the $\dot{V}E/\dot{V}CO_2$ at *AT* of subject 1 differs considerably from that of subject 2. For subjects 2 and 3, although the $\dot{V}E/\dot{V}CO_2$ at *AT* ratios are similar, the $\dot{V}E$-versus-$\dot{V}CO_2$ slopes differ markedly. If $\dot{V}E$ versus $\dot{V}CO_2$ has an intercept at zero on the *y*-axis (subject 3), the $\dot{V}E$-versus-$\dot{V}CO_2$ slope is equal to the $\dot{V}E/\dot{V}CO_2$ at *AT*. (From Sun X-G, Hansen JE, Garatachea N, et al. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med.* 2002;166:1443–1448, with permission.)

from system to system and therefore should be subtracted from $\dot{V}E$ to obtain a value that could allow the measurement to be interrelated among all systems. Elevated ventilatory equivalent values at the *AT* (Fig. 4.22B, C) reflect either hyperventilation or an increase in V_D/V_T (uneven $\dot{V}A/\dot{Q}$). Acute hyperventilation is supported by an abnormally high respiratory exchange ratio. At times, it might be necessary to distinguish between chronic hyperventilation from increased V_D/V_T as a cause of high ventilatory equivalents. Patients with chronic obstructive lung disease (see Fig. 4.22B), restrictive lung disease, LVF, and pulmonary vascular occlusive disease (see Fig. 4.22C) usually have uneven $\dot{V}A/\dot{Q}$. Therefore, their $\dot{V}E/\dot{V}CO_2$ is often high. Because of mechanical limitation to breathing, patients with severe COPD usually do not hyperventilate or increase $\dot{V}E/\dot{V}CO_2$ in response to metabolic acidosis, in contrast to the disorders of $\dot{V}A/\dot{Q}$ without a breathing limitation.

Although the $\dot{V}E/\dot{V}CO_2$ normally increases from the nadir (isocapnic buffering period) to maximal exercise, with the amount depending on the magnitude of the lactic acidosis, it fails to increase above the *AT* if the chemoreceptors for detecting increased H^+ are insensitive (high O_2 breathing) or the work of breathing is high, such as with extreme obesity or severe COPD (see Fig. 4.22).

Differentiating Uneven Ventilation from Uneven Perfusion as the Cause of Uneven $\dot{V}A/\dot{Q}$

Based on the concept that end-tidal expired gas comes from the airways with the longest time constants and

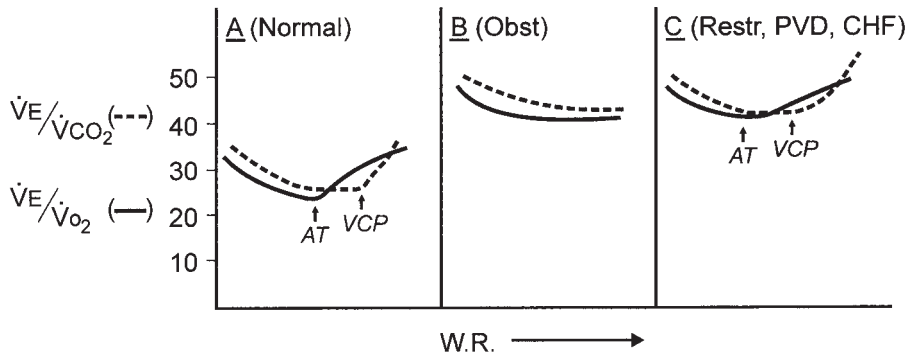

FIGURE 4.22. Typical changes during increasing work rate (WR) in ventilatory equivalent for CO_2 ($\dot{V}E/\dot{V}CO_2$) and O_2 ($\dot{V}E/\dot{V}O_2$) for a normal subject **(A)** and for patients with obstructive **(B)** and restrictive lung or pulmonary vascular disease **(C)**. The nadir in $\dot{V}E/\dot{V}O_2$ reflects the anaerobic threshold (*AT*), and the nadir of the $\dot{V}E/\dot{V}CO_2$ curve occurs between the *AT* and the ventilatory compensation point (VCP).

most poorly ventilated lung acini, the end-tidal CO_2 concentration would be relatively high compared to the mixed expired CO_2 in patients with uneven ventilation. In contrast, patients with uneven perfusion, but uniform ventilation would have reduced end-tidal as well as mixed expired CO_2 concentrations, but the relationship between mixed expired and end-tidal CO_2 concentration would be normal. Thus Hansen et al.[30] studied the mixed expired and end-tidal P_{CO_2}, as well as their ratio in normal subjects and patients with idiopathic pulmonary vasculopathy (idiopathic pulmonary arterial hypertension [PAH]), LVF, and COPD, at rest and during unloaded, *AT* and peak $\dot{V}O_2$ cycling exercise. While mixed expired P_{CO_2} were all comparably reduced relative to normal in all three disorders (Fig. 4.23), end-tidal P_{CO_2} was most reduced in PAH and least reduced in COPD. Despite marked reductions in mixed expired and end-tidal P_{CO_2} in PAH, the P_{ECO_2}/P_{ETCO_2} ratio was normal in PAH. P_{ECO_2}/P_{ETCO_2} was similar to normal and PAH in patients with LVF, but slightly reduced at peak exercise. In contrast, the P_{ECO_2}/P_{ETCO_2} ratio was markedly reduced in COPD, reflecting the long-time constant airways contributing to the end-tidal gas (see Fig. 4.23).

Other Measures of Uneven V/Q

$\dot{V}E$ is a hyperbolic function of CO_2 concentration at a given $\dot{V}CO_2$—that is, $\dot{V}CO_2 = \dot{V}E \times [CO_2]$. Consequently $[CO_2]$ decreases as $\dot{V}E$ increases due to an increase in physiological dead space. Patients with stable LVF have an increase in physiological dead space in proportion to severity of disease.[98] Thus, Matsumoto et al.[46] found a reduction in P_{ETCO_2} during exercise in patients with LVF, the reduction being inversely related to the severity of disease. This is similar to the inverse $\dot{V}E/\dot{V}CO_2$–P_{ETCO_2} relationship found by Yasunobu et al.[112] in patients with idiopathic PAH.

Baba et al.[5] reported that $\dot{V}O_2$ plotted as a log function of $\dot{V}E$ was a good correlate of cardiac function. This has been referred to as the *oxygen uptake efficiency slope*. Apparently, the log function of $\dot{V}E$ was plotted on the *x* axis in order to make the curve more linear, rather than having a physiologic basis. A low slope (higher $\dot{V}E$ relative to $\dot{V}O_2$) occurs with greater mismatching of ventilation relative to $\dot{V}O_2$ and correlated with more severe heart failure. However, Arena et al.[4] found that the oxygen uptake efficiency slope parameter was not as prognostically useful as the previously described $\dot{V}E$ versus $\dot{V}CO$ slope or lowest $\dot{V}E/\dot{V}CO_2$ ratio (at the *AT* or VCP) for evaluating patients with LVF.

Arterial Bicarbonate and Acid–Base Response

Subjects making a maximal effort during a progressively increasing work rate exercise test normally develop a significant metabolic acidosis by the time the terminal work rate is reached. This is observed even for an increasing work-rate exercise test protocol of relatively short duration (8 to 12 minutes) (Fig. 4.24; also see Figs. 2.22 and 2.31). The greatest increase in arterial lactate and reductions in arterial $[HCO_3^-]$ and pH are noted about 2 minutes into recovery (see Fig. 4.23 and Chapters 7 and 10). We find that the 2-minute recovery $[HCO_3^-]$ decreases by at least 6 mmol per L below the resting value if the effort is good and the patient is not limited by a ventilatory or mechanical disorder.

Tidal Volume/Inspiratory Capacity Ratio

Normally, V_T increases during exercise, but it rarely exceeds 80% of the IC, measured during standard resting pulmonary function tests. This ratio may become abnormal during exercise in patients with restrictive lung diseases. Such patients have a reduced IC and limited ability to increase their V_T in response to exercise (see Fig. 4.13C). Thus, as the work rate increases, the V_T/IC ratio reaches a value close to 1.0 at a relatively low work rate. Because a reduced V_T requires a high breathing rate to achieve the V_E needed for CO_2 elimination, we routinely relate V_T to the IC as well as the

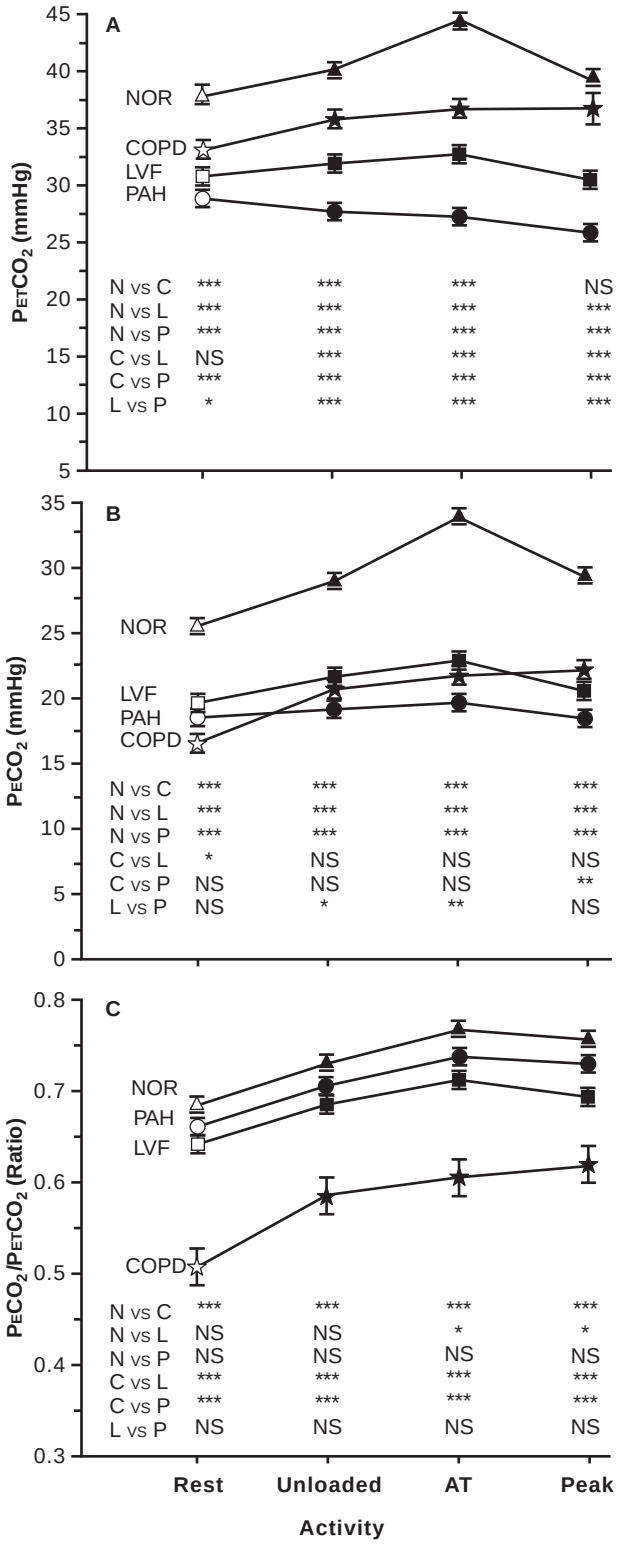

FIGURE 4.23. Values for normal subjects (NOR or N), COPD (or C), left ventricular failure (LVF or L), and pulmonary arterial hypertension (PAH or P) during incremental cycle ergometry tests at rest (*open symbols*), unloaded cycling, anaerobic threshold (*AT*) and peak exercise (*closed symbols*). Values are means ± SEM. **A:** $P_{ET}CO_2$. **B:** P_ECO_2. **C:** $P_ECO_2/P_{ET}CO_2$. *$p < .05$, ** $p < .01$, *** $p < .001$.

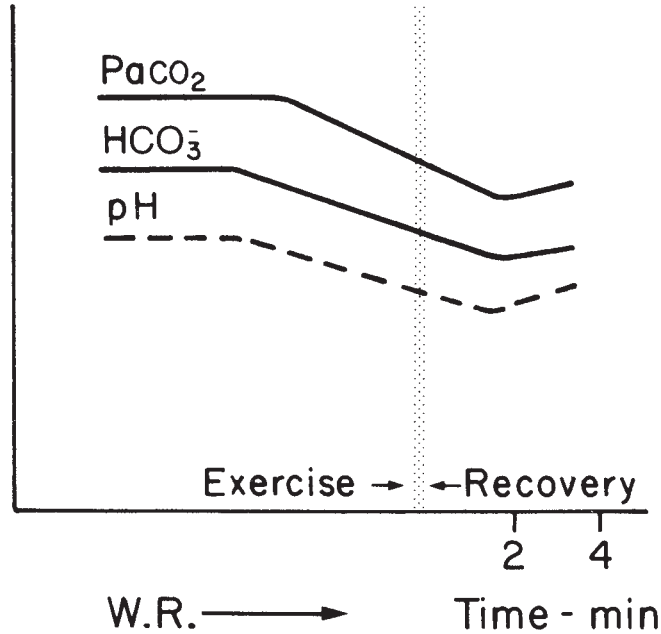

FIGURE 4.24. Normal pattern of change in arterial P_{CO_2}, bicarbonate, and pH as related to increasing work rate and recovery. The stippled vertical bar indicates the point at which exercise stops. Note that the decrease in $Paco_2$ is delayed relative to the decrease in $[HCO_3^-]$ and pH (the period of isocapnic buffering). The arterial P_{CO_2}, $[HCO_3^-]$, and pH continue to decrease in the early recovery period, before starting to increase back toward normal.

ventilatory capacity in panel 9 of the nine-panel plots (Fig 4.32) used to define the patients physiological response to exercise (see Chapter 10). The V_T/IC ratio is more helpful than the V_T/VC ratio because it is very unusual for V_T to exceed IC, even in severe restrictive lung disease.

Measurements Unique to Constant Work Rate Exercise Testing

Whereas the absolute $\dot{V}O_2$ required to perform a given WR should be predictable from the WR, as described in Chapter 2, the ability to supply the O_2 needed to satisfy the O_2 requirement depends on the cardiovascular response. Constant WR tests permit the study of physiological responses by specific organ systems that transport O_2 and CO_2. They also facilitate investigation of control mechanisms. If the constant rate at which work is performed is above the *AT*, then $\dot{V}O_2$ kinetics are slowed and the relation between $\dot{V}O_2$ and $\dot{V}CO_2$ kinetics changes relative to the kinetics for below-*AT* exercise (see Figs. 1.4, 2.37, and 2.38). These changes reflect the patient's cardiovascular status during exercise at the specific WR studied (see Fig. 2.56). The following are useful measurements that can be obtained from the time course of constant WR exercise.

Increase in $\dot{V}O_2$ During Phase I

Normally, oxygen uptake abruptly increases at the start of exercise (phase I) during upright exercise because of the immediate increase in flow of venous blood through the lungs resulting from the increased venous return (Fig. 4.25). The latter is enhanced at the start of exercise by increased cardiac inotropy, compression of veins by contracting muscles, and increased heart rate. Increased pulmonary blood flow is the predominant mechanism accounting for the increase in $\dot{V}O_2$ during the first 15 seconds of exercise. Under conditions in which pulmonary blood flow fails to increase abruptly at the start of exercise, the phase I increase in oxygen uptake is attenuated.[51,68,70,101] A reduced phase I increase in oxygen uptake is found in disorders that limit the increase in pulmonary blood flow at the start of exercise.[51,68,70] A reduced ventilatory response in phase I does not discernibly mask the normal rapid increase in $\dot{V}O_2$.[103]

It should be noted that the phase I increase in $\dot{V}O_2$ is reduced in normal subjects when starting exercise in the supine position because of the lesser increase in stroke volume.[101]

Oxygen Uptake Kinetics Above or Below the Anaerobic Threshold

After the phase I immediate (first 15 seconds of exercise) increase in $\dot{V}O_2$ and $\dot{V}CO_2$ in a constant work-rate test, $\dot{V}O_2$ and $\dot{V}CO_2$ increase as exponential functions (phase II). Therefore, their rates of rise have been described by time constants (i.e., the time for 63% of the final response to be reached). Although this single-exponential approach has been used by some investigators,[23,33,44,110] it is not a totally accurate measurement because $\dot{V}O_2$ has first-order exponential kinetics only for work rates below the *AT*. Above the *AT*, the $\dot{V}O_2$ kinetics must be defined by at least two exponential functions, the second becoming more prominent the higher the work above the *AT*.[9,110]

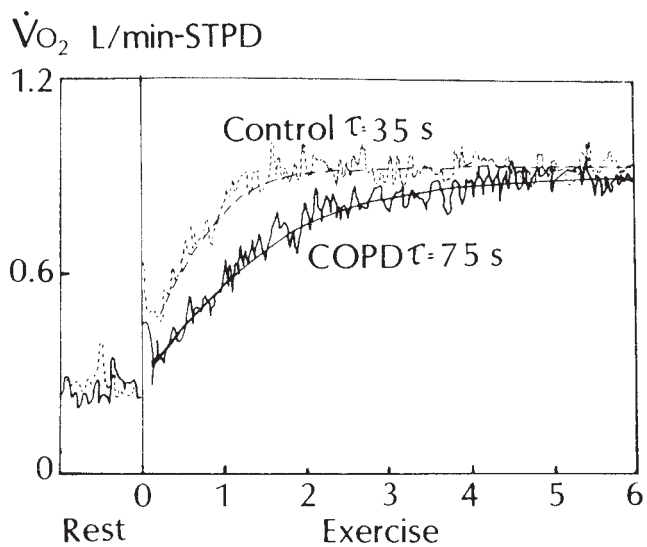

FIGURE 4.25. Pattern of oxygen uptake ($\dot{V}O_2$) in a patient with chronic obstructive pulmonary disease (COPD) and a matched normal subject during the performance of a constant 40-W cycle ergometer exercise. Note that $\dot{V}O_2$ during phase I (the first 15 seconds of exercise) is less and the rate of rise of $\dot{V}O_2$ to its asymptote during phase II is slower in the COPD patient. The latter is reflected in the longer time constant (*τ*), as compared with a normal control subject. (Data from Nery LE, Wasserman K, Andrews JD, et al. Ventilatory and gas exchange kinetics during exercise in chronic airways obstruction. *J Appl Physiol.* 1982;53:1594–1602.)

Figure 4.25 shows the pattern of oxygen uptake kinetics as related to fitness for a normal subject and a patient with COPD. For the same relatively low work rate (40-W cycling work), the $\dot{V}O_2$ for the patient with COPD had a longer time constant than that of the normal subject (matched for age and gender). When the time constant for the increase in $\dot{V}O_2$ for the control (normal) subject is compared to that of the COPD patient, the increase in $\dot{V}O_2$ is slower for the COPD patient. This indicates an increased O_2 deficit and implies that a lactic acidosis developed to support the bioenergetics of the O_2 deficit period.

Increase in $\dot{V}O_2$ Between 3 and 6 Minutes of Exercise

When the exercise work rate is below the subject's *AT* (i.e., the subject is in metabolic steady state), the $\dot{V}O_2$ after 3 minutes (phase III) is constant. However, for work rates above the *AT*, $\dot{V}O_2$ increases after 3 minutes in proportion to the increase in lactate.[63,92,110,117] The increase in $\dot{V}O_2$ between 3 and 6 minutes of exercise [$\Delta\dot{V}O_2$ (6 – 3)] can be determined by linear regression of the $\dot{V}O_2$ between 3 and 6 minutes of exercise (Fig. 4.26). When $\Delta\dot{V}O_2$ (6 – 3) is correlated with the increase in lactate above rest, a good correlation is found for both chronic heart failure patients and normal subjects (Fig. 4.27). The regression of the relationship goes through the origin, suggesting that confounding factors do not override the importance of lactate increase in the development of this slow component in $\dot{V}O_2$ when performing constant work rate exercise above the *AT*.

Suprathreshold Work Rate and Endurance Time

For sustained constant work rate exercise below the *AT*, ATP regeneration is achieved aerobically. Therefore, the exercising muscle groups perform without anaerobic metabolism (anaerobic glycolysis with lactate production by the exercising muscle and its catabolism by the liver, nonexercising muscle and other organs capable of converting lactate to pyruvate, and other metabolic

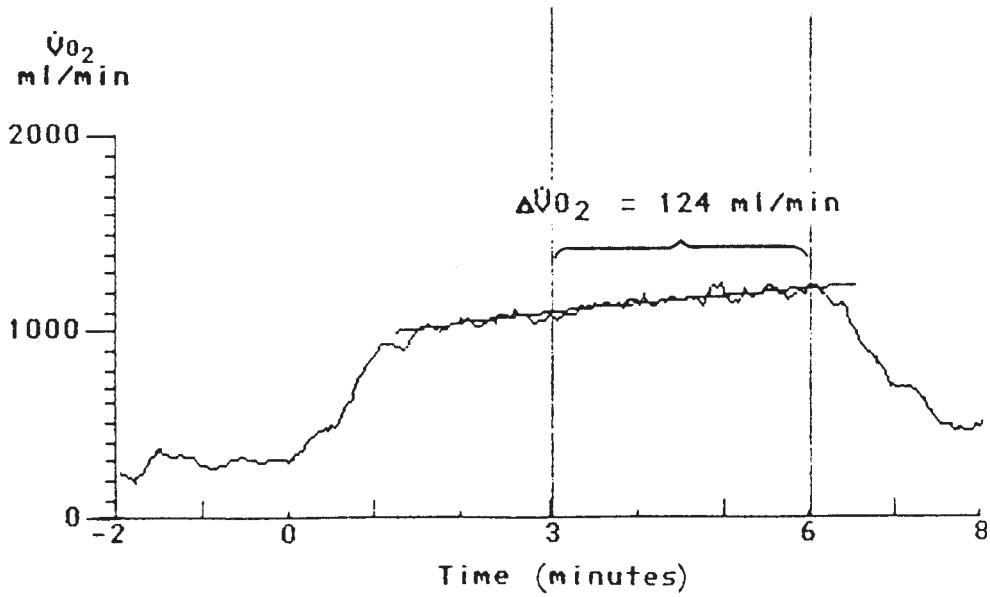

FIGURE 4.26. Method illustrating the measurement of the difference in oxygen uptake ($\dot{V}O_2$) between 3 and 6 minutes [$\Delta\dot{V}O_2$ (6 – 3)] of constant work rate exercise (70 W) in a patient with cardiac disease. The straight line drawn on the plot between 3 and 6 minutes was determined by the best least square fit for the breath-by-breath data. The difference in $\dot{V}O_2$ at the 6- and 3-minute points is calculated from the 3- and 6-minute intercepts of the linear regression of the data between 3 and 6 minutes.

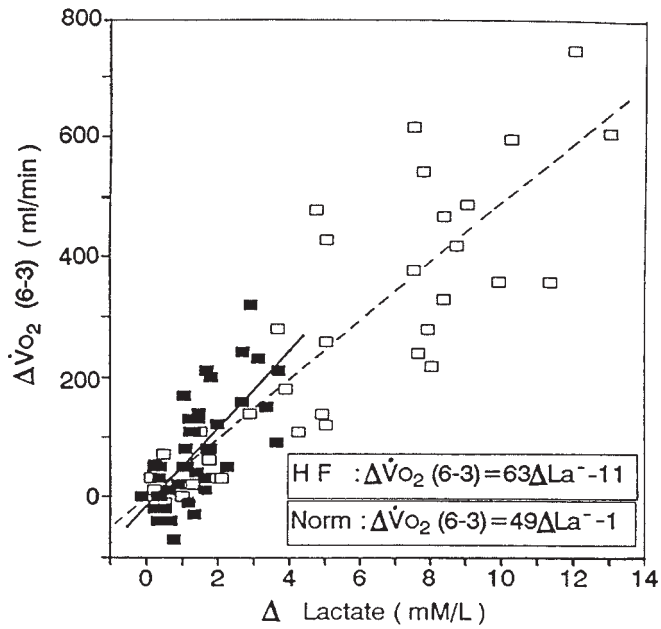

FIGURE 4.27. Degree of non–steady-state in oxygen uptake ($\dot{V}O_2$), expressed as the increase in $\dot{V}O_2$ between 3 and 6 minutes [$\dot{V}O_2$ (6 – 3)], as a function of the increase in blood lactate above rest in normal subjects (*open squares*) and in patients with heart failure (*solid squares*). The blood was sampled from the antecubital vein at rest and at 2 minutes of recovery. Neither the slopes nor the intercepts of the regression equations differed significantly between the two groups. (From Roston WL, Whipp BJ, Davis JA, et al. Oxygen uptake kinetics and lactate concentration during exercise in man. *Am Rev Respir Dis.* 1987;135:1080–1084 and Zhang YY, Wasserman K, Sietsema KE, et al. O_2 uptake kinetics in response to exercise: a measure of tissue anaerobiosis in heart failure. *Chest.* 1993;103: 735–741.)

intermediaries in equilibrium with pyruvate). ATP from splitting of PCr is limited and depleted early during the oxygen deficit period of exercise (primarily during the first minute of exercise). Exercise above the *AT* cannot be sustained when anaerobic glycolysis is no longer a source for ATP regeneration. To sustain prolonged constant WR exercise, the source of for ATP regeneration must be aerobic metabolism.

The Power-Duration Relationship

Whipp clarified the relationship between exercise power and exercise duration for work powers above the *LT*.[105] The concept is that work performed above the *AT* would be foreshortened when the anaerobic sources of bioenergetics are depleted. The longer time to fatigue reflects a proportional shift from anaerobic to aerobic metabolism. Thus a series of constant suprathreshold WR tests allows the investigator to evaluate relative fitness to sustain anaerobic work.

Mean Response Time

Sietsema et al.[71] performed multiple 6-minute constant WR tests in normal subjects at WRs ranging from unloaded cycling to 150 W. These investigators assumed single-exponential kinetics and calculated a mean response time (MRT) for the data. The MRT measurement at the higher WRs allowed discrimination of the subject's fitness to perform a progressively increasing WR test. Thus, the subjects with the highest $\dot{V}O_2$ max per kilogram body weight had the lowest MRTs for the 75-, 100-, and 150-W WRs (see Fig. 2.56).

Combining $\dot{V}O_2$ and $\dot{V}CO_2$ Kinetics for Detecting Anaerobic Metabolism and Lactic Acid Buffering

For above-*AT* constant WR exercise, $\dot{V}CO_2$ increases more rapidly than $\dot{V}O_2$ after about 1 to 2 minutes (see Fig. 1.4). This is primarily due to the buffering of newly formed lactic acid by HCO_3^-. Thus, from the simultaneous analysis of $\dot{V}CO_2$ and $\dot{V}O_2$, it is possible to determine whether the WR is accompanied by a lactic acidosis.

By measuring CO_2 output and O_2 uptake breath by breath for work above unloaded cycling exercise, Zhang et al.[116] demonstrated that the cumulative output of CO_2 progressively increases relative to the cumulative increase in O_2 uptake for constant WR exercise associated with a lactic acidosis, in contrast to work for which a lactic acidosis was not present (Fig. 4.28). By multiplying $\dot{V}O_2$ by the muscle substrate respiratory quotient (on average approximately 0.95), the aerobic CO_2 production was calculated. The difference between the total CO_2 output and the aerobic CO_2 output should represent the CO_2 output from buffering lactic acid plus CO_2 from hyperventilation, if any (see Fig. 4.28). The latter accounted for only about 6% of the excess CO_2 over that derived from aerobic metabolism in subjects who hyperventilated in response to the exercise-induced lactic acidosis at 6 minutes of exercise. When the number of millimoles of CO_2 output derived from the buffering of lactic acid at 6 minutes of constant WR exercise was calculated, this quantity correlated closely with the lactate concentration increase determined from antecubital vein blood sampled 2 minutes into recovery (Fig. 4.29). This method therefore describes a noninvasive estimate of the *magnitude* of

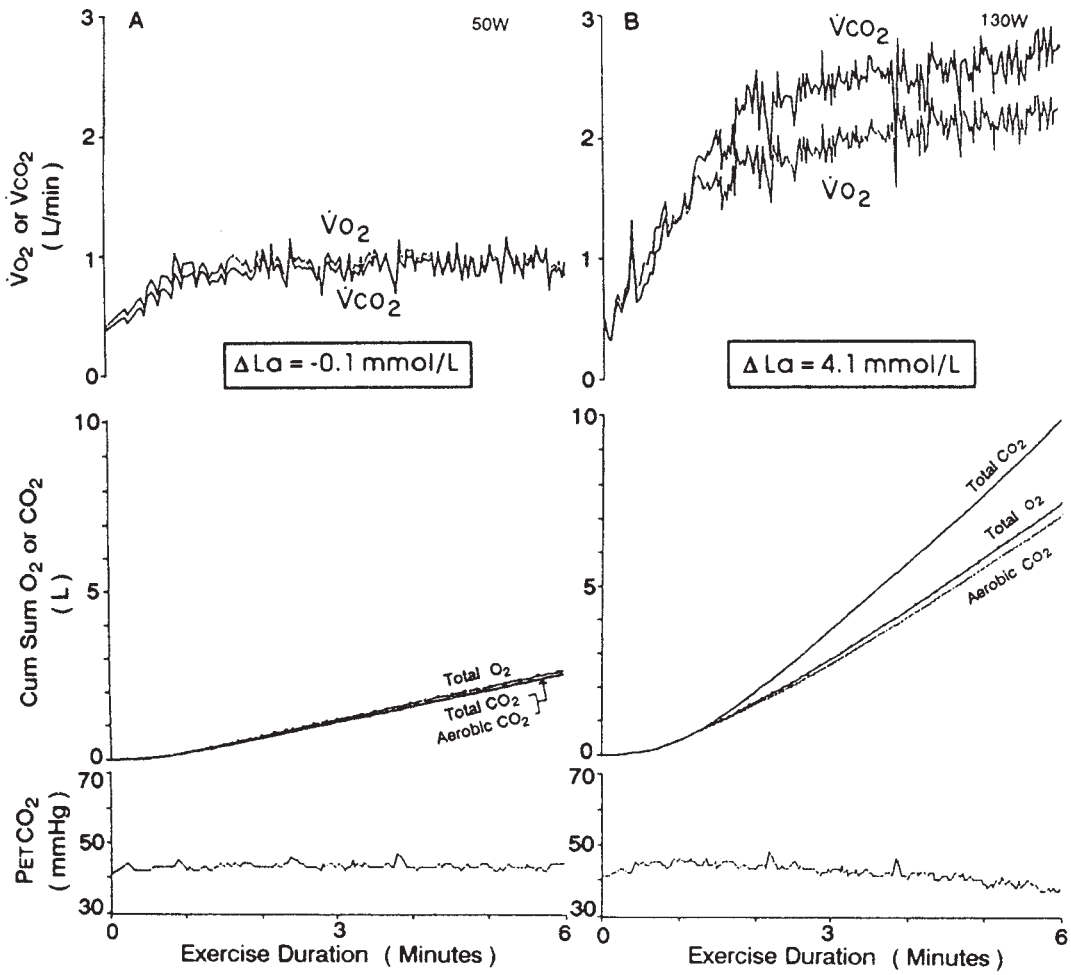

FIGURE 4.28. Breath-by-breath changes in $\dot{V}O_2$, $\dot{V}CO_2$, total or accumulated O_2 uptake (Cum Sum O_2), total or accumulated CO_2 output (Cum Sum CO_2), aerobic CO_2 output ($\dot{V}O_2 \times 0.95$), and $P_{ET}CO_2$ in response to 50-W (A) and 130-W (B) work-rate tests for one subject. The difference between the accumulated total CO_2 output and aerobic CO_2 output is the accumulated buffer CO_2 output. In panel A, the total and aerobic Cum Sum CO_2 curves overlap and cannot be distinguished. The increase in antecubital vein lactate at the end of 6 minutes of exercise for each study is shown. (From Zhang YY, Sietsema KE, Sullivan CS, et al. A method for estimating bicarbonate buffering of lactic acid during constant work rate exercise. *Eur J Appl Physiol.* 1994;69:309–315, with permission.)

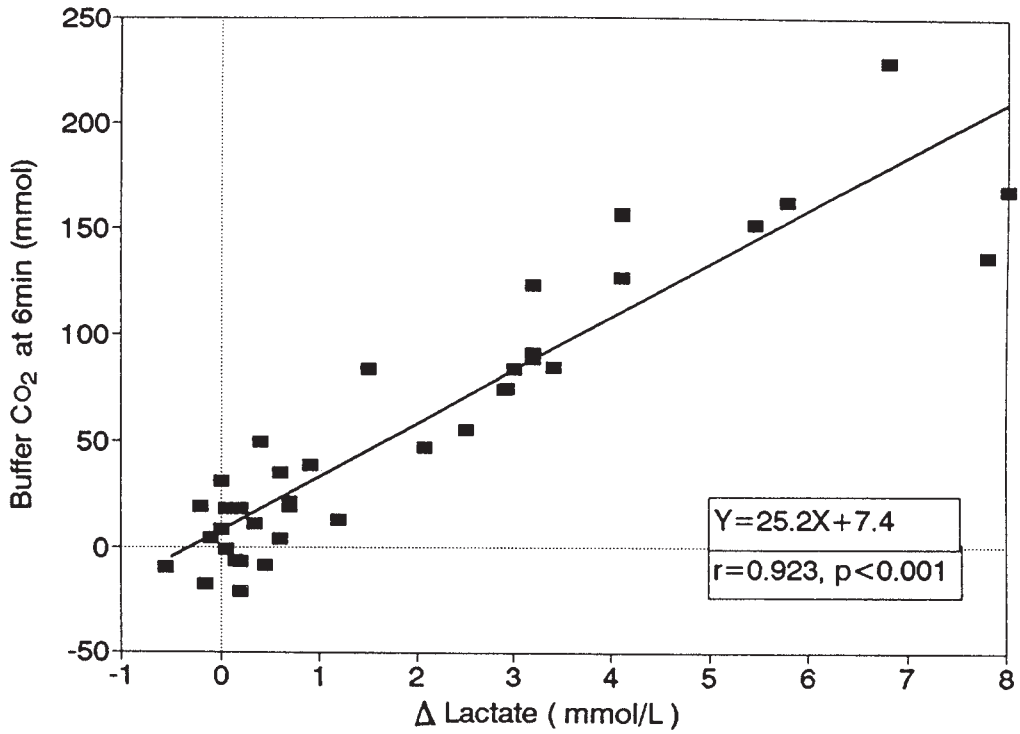

FIGURE 4.29. Buffer CO_2 (mmol) as a function of the increase in blood lactate concentration (La^-) at the end of 6 minutes of exercise. The correlation coefficient, significance of the correlation, and the equation for the regression are shown. (From Zhang YY, Sietsema KE, Sullivan CS, et al. A method for estimating bicarbonate buffering of lactic acid during constant work rate exercise. *Eur J Appl Physiol.* 1994;69:309–315, with permission.)

HCO_3^- decrease or lactate increase at the end of 6 minutes of constant WR exercise. The slope of the regression line defines the volume of distribution of lactate (25 L, or about one-third body weight for the population of adult subjects studied).

In a steady state below the *AT*, no anaerobic mechanisms support bioenergetics, and the O_2 debt has reached a maximum.[66] However, constant WR exercise performed above the *AT* results in a delay or an inability to achieve total aerobic energy generation (steady-state $\dot{V}O_2$ without increasing the O_2 deficit; see Figs. 2.37 and 2.38). Thus, $\dot{V}O_2$ continues to increase for exercise above *AT* after 3 minutes, the rate of increase depending on the fractional distance between *AT* and $\dot{V}O_2$ max (Fig. 4.30). To determine if a specific WR is above the *AT*, measurement of $\dot{V}O_2$ at 3 and 6 minutes during a 6-minute constant WR test is helpful. Measurement of $\dot{V}CO_2$ simultaneously with $\dot{V}O_2$ provides confirmation that the WR is above the *AT*.

Carotid Body Contribution to Ventilation

Several techniques have been proposed to determine the contribution of the carotid bodies to the exercise ventilatory response.[60,67] A modified Dejours test,[22] performed during moderate constant WR exercise,[74,111] is informative and applicable to patients with lung diseases (Fig. 4.31). It was found that 100% O_2 attenuates the carotid body output.[97] Therefore, in the steady state of an air-breathing exercise test, the surreptitious switch to 100% oxygen results in an almost immediate decrease in ventilation (within one or two breaths) if the carotid bodies actively contribute to ventilatory drive. This decrease reflects the carotid body contribution to the ventilatory drive and can be expressed as a percentage of the pre–O_2 breathing ventilation. Ventilation decreases to a nadir by 15 seconds. Once the nadir is reached, ventilation starts increasing back toward, but not completely to, its control value despite continued breathing of 100% O_2. The most likely stimulus for this rebound in $\dot{V}E$ is the increase in $PaCO_2$ caused by the abrupt decrease in $\dot{V}E$ resulting from O_2 breathing. Whereas hyperoxia continues to inhibit carotid body drive to ventilation, the increase in $PaCO_2$ resulting from the inhibition stimulates the central chemoreceptors, partially masking the carotid body ventilatory drive. If ventilation is not measured breath by breath, the magnitude of the carotid body contribution to the exercise ventilatory stimulus is inadequately quantified. The advantages of this test are its brevity, its applicability at work rates below or above the *AT*, and its safety, in contrast to breathing hypoxic gas mixtures to stimulate the carotid bodies.[22]

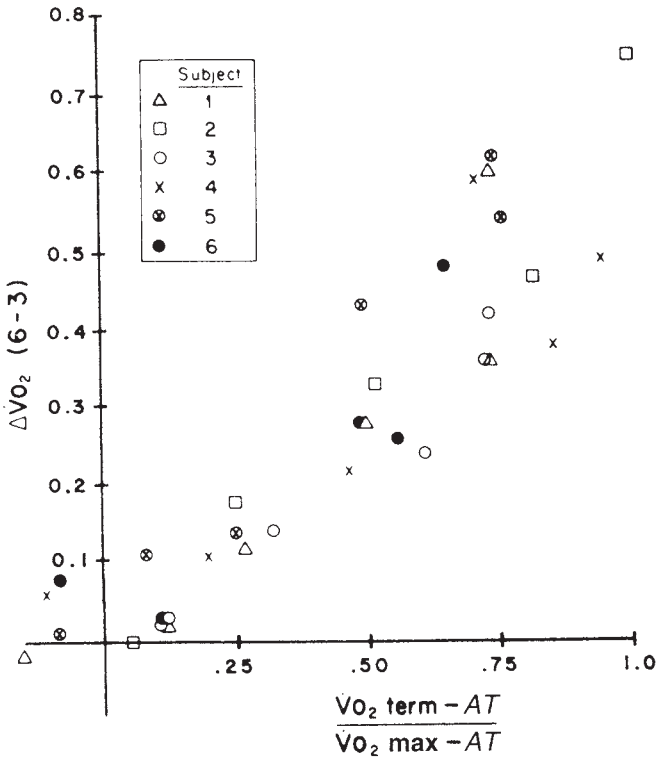

FIGURE 4.30. Difference between 6- and 3-minute $\dot{V}O_2$ (L) for constant work rate exercise [$\Delta\dot{V}O_2$ (6 – 3)] as related to the ratio of the difference between the $\dot{V}O_2$ asymptote at the termination of exercise ($\dot{V}O_2$ term) and the anaerobic threshold (*AT*) and the differences between the $\dot{V}O_2$max and the *AT* in six normal subjects. (Modified from Roston WL, Whipp BJ, Davis JA, et al. Oxygen uptake kinetics and lactate concentration during exercise in man. *Am Rev Respir Dis.* 1987;135:1080–1084.)

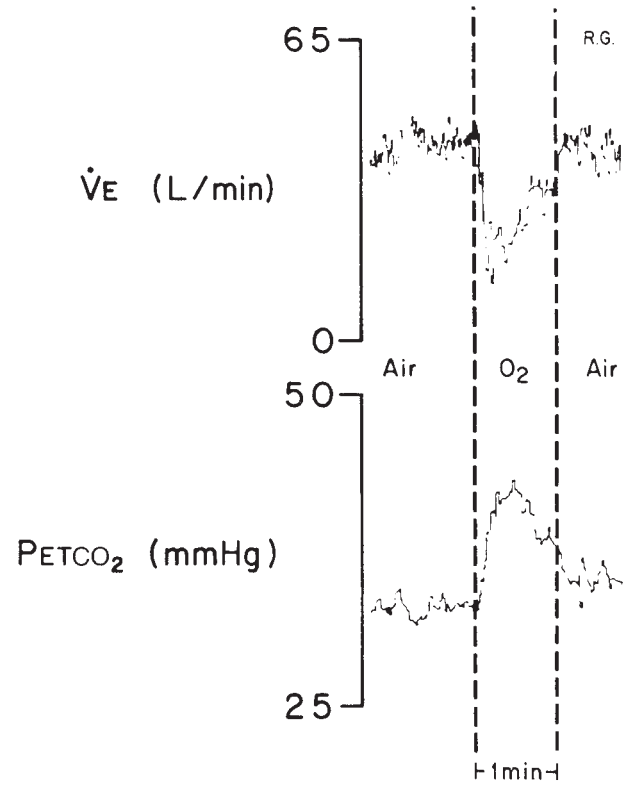

FIGURE 4.31. Illustration of a safe test for assessing carotid body contribution to ventilation during exercise. The study is that of a patient with pulmonary alveolar proteinosis with a Pao_2 of 54 during exercise. A work rate is selected at which the patient can perform without difficulty and for which a steady state in ventilation is reached by 4 to 5 minutes. When $\dot{V}E$ is constant, the inspired gas is switched from air to 100% oxygen for 1 minute. $\dot{V}E$ decreases to a nadir within several breaths, and, as a consequence, $PETCO_2$ rises. After 15 seconds, $\dot{V}E$ spontaneously starts to rebound toward the air-breathing value, presumably because of CO_2 stimulation of central chemoreceptors. By 45 seconds, $\dot{V}E$ becomes relatively constant at a reduced value, and $PETCO_2$ levels off at an elevated value as compared to the control period. Thus, three phases in ventilation are observed when switching to 100% oxygen breathing: the first 15 seconds, when the carotid bodies are attenuated maximally; the period between 15 and 45 seconds, which shows a rebound in $\dot{V}E$ presumably caused by the increase in arterial Pco_2; and the period after 45 seconds, when $\dot{V}E$ and $PETCO_2$ reach constant values. The abrupt changes in $\dot{V}E$ in response to the O_2 switch and return to air breathing reflect the rapid control exerted by the carotid bodies in the regulation of ventilation. (From Wasserman K, Whipp BJ, Davis JA. Respiratory physiology of exercise: metabolism, gas exchange, and ventilatory control. In: Widdicombe JG, ed. *International Review of Physiology III.* Baltimore, MD: University Park Press; 1981:149–211, with permission.)

DATA DISPLAY AND INTERPRETATION

CPET studies have taught us that different defects in the coupling of external (airway) to cellular (mitochondrial) respiration will affect gas exchange in different ways. Thus, the pattern of gas exchange at the airway can be used to diagnose pathophysiology and to support or refute the correctness of a clinical diagnosis. With an appropriate display of the data, it is possible to noninvasively determine the functional status of the cardiovascular system and the ventilatory system, as well as the uniformity of matching of ventilation to blood flow. Because graphical displays are much easier to interpret than tabular displays, we transform the CPET data into a graphical display of nine panels on a single page containing 16 graphs. These graphs are systematically arranged to assess cardiovascular, ventilatory, ventilation–perfusion matching, and metabolic responses to exercise (Fig. 4.32). In addition, parameters of pulmonary function and target values such as predicted $\dot{V}O_2$max and maximum heart rate are displayed on relevant plots. Normal values for all the measurements in the nine-panel graphical array are summarized in Chapter 7 and are reported in summary tables in the cases of Chapter 10. The systematic approach, using flowcharts leading to interpretation and specific diagnoses, is described in Chapter 8.

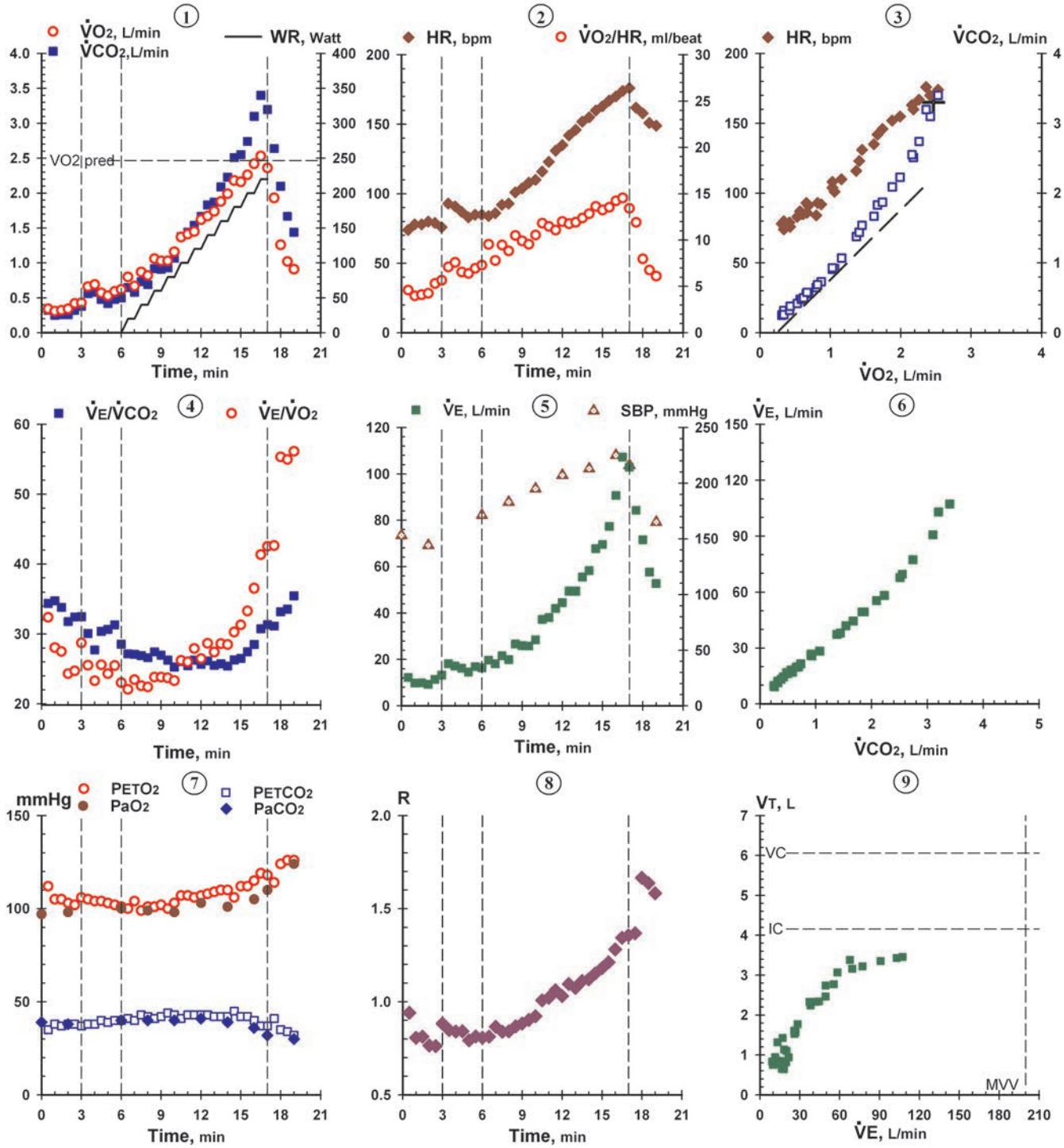

FIGURE 4.32. Nine-panel graphical array used to describe the cardiovascular, ventilatory, ventilation-perfusion matching, and metabolic responses to exercise. The study is from a 55-year-old male patient. The responses are normal. The diagonal line drawn on panel 1 is the slope of the normal increase in $\dot{V}O_2$ for the work rate increase (10 mL/min/W). The × in panel 3 is the predicted peak $\dot{V}O_2$ and predicted peak heart rate (HR). $\dot{V}E$, minute ventilation; $\dot{V}O_2$/HR, O_2 pulse; MVV, maximal voluntary ventilation; IC, inspiratory capacity; VC, vital capacity; R, respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$); $PETO_2$, end-tidal PO_2; $PETCO_2$, end-tidal PCO_2; PaO_2, arterial PO_2; $PaCO_2$, arterial PCO_2. (Modified from Case 1 in Chapter 10.)

Evaluation of Systemic Function from the Nine-Panel Graphical Array

The questions that can be asked of progressively increasing work-rate exercise tests are shown in Table 4.1. Using Figure 4.32 to illustrate the use of the nine-panel graphical array, the answer to the first question relating to exercise capacity is addressed in panel 1 from the measurement of maximal (peak) $\dot{V}O_2$. If peak $\dot{V}O_2$ is reduced, we ask if the reduction is due to a cardiovascular limitation (panels 1, 2, and 3), ventilatory limitation (panels 1, 5, 7, and 9), ventilation–perfusion mismatching (panels 1, 4, 6, and 7), or abnormality in use of metabolic substrate (panels 1 and 8). The nine panels illustrated in Figure 4.32 describe the following physiology:

- *Panel 1:* $\dot{V}O_2$ and $\dot{V}CO_2$ versus time and work rate, and slope showing predicted rate of increase in $\dot{V}O_2$ for the work rate increase (diagonal or one-minute step line). This is the first panel to address when interpreting if a patient is limited in exercise performance, because this plot gives a global assessment of exercise performance and the presence of exercise limitation. The $\Delta\dot{V}O_2/\Delta WR$ is commonly abnormal in patients with cardiovascular disease, with the pattern varying with the defect (e.g., heart disease, peripheral arterial disease, pulmonary vascular disease). The different patterns are described in Chapters 5, 9, and 10. The $\dot{V}CO_2$ increases faster than the $\dot{V}O_2$ above the *AT* even when the rate of $\dot{V}O_2$ increase is reduced.
- *Panel 2:* Heart rate (HR) and $\dot{V}O_2$/HR (O_2 pulse = stroke volume × arteriovenous O_2 difference) versus time and work rate. HR is high and $\dot{V}O_2$/HR is low for a given work rate in patients with certain cardiovascular defects. With chronotropic incompetence or β-adrenergic blockade without systolic or diastolic dysfunction, the O_2 pulse could be normal or high.
- *Panel 3:* HR versus $\dot{V}O_2$, and $\dot{V}CO_2$ versus $\dot{V}O_2$. In normal subjects, HR increases linearly with $\dot{V}O_2$ to their predicted maximums (indicated with an *x*). In patients with heart failure, without chronotropic incompetence, the increase is steep. The relationship may lose its linearity, with HR increasing progressively more rapidly than $\dot{V}O_2$ in patients with myocardial ischemia. The patient's O_2 pulse can be determined from the intersection of the patient's data with plots of HR–$\dot{V}O_2$ isopleths through the origin.

  In the second graph in this panel, $\dot{V}CO_2$ increases linearly with $\dot{V}O_2$ with a slope of 1, or slightly less than 1, up to the *AT* (*S1*). Then $\dot{V}CO_2$ increases more rapidly above *AT*, causing a steepening of the slope (*S2*). The degree of the steepening of *S2* depends on the rate of HCO_3^- buffering of lactic acid. The break point describes the *AT*. This is the V-slope method for determining *AT*.[11] It is low in patients with poor cardiovascular function.
- *Panel 4:* Ventilatory equivalent for O_2 and CO_2 ($\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$) versus time and work rate. $\dot{V}E/\dot{V}O_2$ decreases to a nadir at the *AT*. $\dot{V}E/\dot{V}CO_2$ decreases to a nadir in the period between the *AT* and the VCP. Both values are high in diseases with uneven ventilation-perfusion relationships (increased VD/VT).
- *Panel 5:* $\dot{V}E$ versus time and work rate. This plot normally becomes curvilinear as work rate is increased above the *AT*, except when $\dot{V}E$ is limited by obesity or obstructive lung disease. Also plotted on this panel is systolic blood pressure at rest and during exercise.
- *Panel 6:* $\dot{V}E$ versus $\dot{V}CO_2$ plotted on a scale of 30:1. This plot yields a linear relationship until ventilatory compensation for metabolic acidosis steepens the plot. The slope of the linear part is steeper above the VCP than below, resulting from the increased arterial H^+ stimulus from accumulating lactic acid. The slope is abnormally steep when the exercise physiological dead space/tidal volume ratio is increased.
- *Panel 7:* $PETCO_2$, $PETO_2$, and SpO_2 (arterial oxyhemoglobin saturation determined with a pulse oximeter) versus time and work rate. Low $PETCO_2$ signals either hyperventilation or high $\dot{V}A/\dot{Q}$ mismatching. R (panel 8) reveals if hyperventilation is acute. Arterial blood gases or knowledge of plasma HCO_3^- differentiates chronic hyperventilation from $\dot{V}A/\dot{Q}$ abnormality in patients with a low $PETCO_2$. Arterial blood gases are also plotted on this graph to detect the presence of high and low $\dot{V}A/\dot{Q}$ mismatching and to determine the presence and severity of arterial hypoxemia and hypercapnia.
- *Panel 8:* Respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$, R) versus time and work rate. This plot usually starts at approximately 0.8 and increases to values higher than 1.0 above the *AT*. Inability or failure to produce an exercise lactic acidosis would mitigate an increase in R to values above 1.0, except when accompanied by acute hyperventilation (decreased $PaCO_2$). Acute hyperventilation at rest or low work rates, as reflected by a decreasing $PETCO_2$, yields an R greater than 1.0.
- *Panel 9:* Tidal volume (VT) versus $\dot{V}E$. The patient's vital capacity (VC) and IC are shown on the vertical axis, and actually measured MVV or $FEV_1 \times 40$ is shown on the horizontal axis. Ventilatory frequency can be plotted as isopleths through the origin. With airflow limitation, maximal exercise $\dot{V}E$ approximates the MVV, resulting in a low breathing reserve (MVV – $\dot{V}E$). The breathing reserve cannot be predicted from resting pulmonary function measurements alone. With restrictive lung disease, VT may approximate the IC at low work rates, and respiratory rate may increase to 50 or 60, in contrast to the lower values seen in patients with COPD.

Factors Confounding Interpretation of Cardiopulmonary Exercise Testing

Three physiological derangements, not usually considered as diseases of the cardiorespiratory system, may contribute significantly to exercise intolerance. These physiological

derangements are obesity, anemia, and carboxyhemoglobinemia as secondary to cigarette smoking.

Obesity adds to the O_2 and cardiac output cost of exercise. It may also restrict the ventilatory system and increase the work of breathing. The restriction of ventilatory capacity caused by obesity is more marked as the $\dot{V}E$ requirement increases, possibly leading to hypercapnia.

Anemia reduces the arterial O_2 content and the maximal arteriovenous O_2 content difference. Therefore, to achieve a given $\dot{V}O_2$, a greater cardiac output is required than if anemia were not present. Also, because the O_2 content of the arterial blood is reduced, the capillary PO_2 decreases to its critical value, inducing anaerobic metabolism and lactic acidosis at a lower than normal work rate and $\dot{V}O_2$.

The carboxyhemoglobin level in the blood of the heavy cigarette smoker may reach 10% to 12%. This not only reduces the arterial O_2 content to a level that would be normally found with an arterial PO_2 of about 50 to 55 mm Hg, but also shifts the oxyhemoglobin dissociation curve to the left, making it more difficult for O_2 to dissociate from hemoglobin at a given PO_2. Thus, the capillary PO_2 falls more rapidly to its critical value, resulting in a lactic acidosis at a reduced level of work.[43]

The net effect of each of these complicating factors is a reduction in the amount of external work that the patient can perform. However, in moderate obesity, the maximal $\dot{V}O_2$ and *AT* might be normal or high when referenced to the patient's ideal body weight. In contrast, the maximal $\dot{V}O_2$, *AT*, and peak work rate are reduced in patients with anemia and increased carboxyhemoglobinemia.

SUMMARY

Changes in O_2 uptake and CO_2 output by the lungs reflect changes in cell respiration induced by exercise. Although the source of the increased gas exchange with exercise is the increase in cell respiration, cardiac output and ventilation modulate the gas exchange at the airway. Thus, diseases of the cardiovascular and ventilatory systems will affect the gas exchange pattern at the airway, depending on the disease pathophysiology. Measurements that assess these functions, following controlled work-rate perturbations, define the physiologic state of the organ systems that participate in gas transport. Defects in the coupling of external to internal respiration result in gas exchange abnormalities characteristic of the limiting organ system. For example, whereas diseases of the heart, the lungs, and the peripheral and pulmonary circulations all result in demonstrable abnormalities in gas exchange, each disorder manifests specific and relatively unique abnormalities that are amplified by exercise testing. The effects of various disease states on these measurements are described in Chapter 5.

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CHAPTER

5

Pathophysiology of Disorders Limiting Exercise

The coupling of external to cellular respiration to perform exercise involves many organ systems. From Figure 5.1, it is evident that the blood, the peripheral circulation, the heart, the pulmonary circulation, the lungs, the chest wall, respiratory control, and metabolic pathways in bioenergetics influence the normal coupling of external to cellular respiration. Thus, defects of any might limit exercise performance. The objective of this chapter is to describe the changes in external respiration that characterize the pathophysiology brought about by diseases of the organ systems that are required for the support of the exercise bioenergetic mechanisms. These disorders are listed by class in Table 5.1, accompanied by statements of major pathophysiology and physiological limitation. Individually or in combination, these disorders limit exercise by causing symptoms of dyspnea, fatigue, and/or pain.

OBESITY

Although the obese subject has some increase in resting metabolic rate ($\dot{V}o_2$) relative to lean body mass, the increase is more marked during dynamic exercise (see Figs. 2.7 and 4.5; Table 5.2). Additional energy is needed to move heavy legs in leg cycling exercise or a large body mass while ambulating. This adds to the O_2 needed to perform external work in proportion to the excess body weight (Fig. 5.2).[31,78] Because the metabolic rate is increased to perform external work, obese people require an increased cardiorespiratory response to exercise. However, the heart, blood vessels, lungs, and muscles do not usually increase in size commensurate with the subject's added weight. Consequently, for the obese individual to do any amount of physical work, there must be greater than normal cardiovascular and ventilatory responses. Because more O_2 transport than normal is needed to support body movement, less O_2 transport is available for effective external work in obesity.

Constraints are imposed on the maximal exercise performance because of altered cardiovascular and ventilatory mechanics in obesity, especially in the extremely obese subject. Because of the large mass, the resting cardiac output per kilogram of lean body weight is already high.

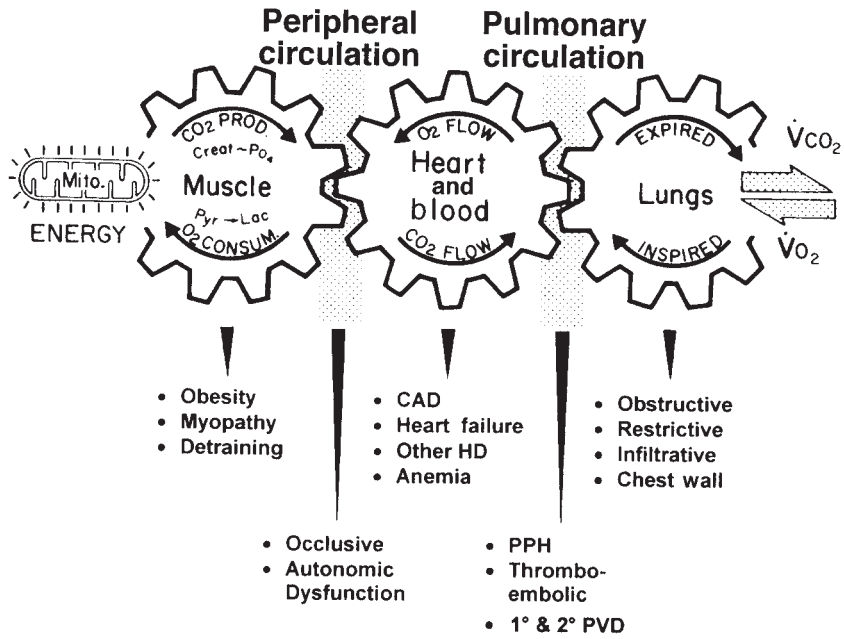

FIGURE 5.1. Sites of interference in the metabolic-cardiovascular-ventilatory coupling caused by various disease states. CAD, coronary artery disease; HD, heart disease; PPH, primary pulmonary hypertension; PVD, pulmonary vascular disease.

Thus, the cardiac output reserve available to support the increased muscle O_2 requirement for exercise is reduced.[4] Furthermore, the added mass on the chest wall and the increased pressure in the abdomen cause an increase in ventilatory work. In very obese subjects, the increased abdominal pressure may constrain diaphragmatic descent during inspiration, reducing the inspiratory capacity and tidal volume. Both the increased abdominal pressure and the added weight to the chest wall effectively "chest straps" the obese patient,[5,19,26,60] causing the resting end-expiratory lung volume (functional residual capacity [FRC]) to be reduced (in extreme cases, close to the residual volume).[56] This can lead to atelectasis of peripheral lung units and hypoxemia at rest. In addition, pulmonary vascular resistance may be increased, primarily as a result of pulmonary insufficiency. Thus, cor pulmonale may develop with hypoxemia, secondary erythrocytosis, hepatomegaly, peripheral edema, and right ventricular hypertrophy and/or failure.

The increased O_2 cost of performing mechanical work is predictable and well worked out for cycle ergometry.[31,78] The $\dot{V}O_2$–work rate relationship is displaced upward, depending on the degree of obesity, by 5.8 mL/min/kg (Fig. 5.2). However, obesity causes no discernible change in the slope of the $\dot{V}O_2$–work rate relationship.[31,78] The effect of adipose tissue distribution in the body (i.e., legs or trunk) on $\dot{V}O_2$ has not been investigated.

The maximum $\dot{V}O_2$ and anaerobic threshold (*AT*) are low when related to actual body weight, but usually normal or high when related to height[31] or to predicted weight or lean body mass.[12] Because of the high metabolic cost of doing even modest levels of exercise, an active, otherwise healthy, obese subject may have good cardiovascular fitness but reduced work capacity. Thus, the actual $\dot{V}O_2$max, based on height or lean body weight, may be greater than that predicted for a normal sedentary subject.

The hypoxemia commonly present at rest in the obese subject results from atelectasis of peripheral lung units. This usually improves during exercise, because the deep breathing re-expands atelectatic lung units. It is the only pulmonary condition in which arterial oxygenation improves during exercise. Because ventilation–perfusion relationships usually normalize during exercise in the patient with uncomplicated obesity, V_D/V_T, $P(A-a)O_2$, and $P(a-ET)CO_2$ values are usually normal during exercise. However, ventilatory compensation for the lactic acidosis of exercise is usually absent at peak $\dot{V}O_2$ because of the increased work of breathing in the obese subject.

OVERVIEW OF SPECIFIC PATTERNS OF $\dot{V}O_2$ RESPONSE TO INCREASING WORK RATE ($\Delta\dot{V}O_2/\Delta WR$) IN PATIENTS WITH CARDIOVASCULAR ABNORMALITIES

Before discussing each major class of heart disease, it is noteworthy to consider features in common with all forms of heart disease. An example of a normal $\dot{V}O_2$ increase relative to the work rate increase (10 mL/min/W) is illustrated in Figure 5.3A. If the circulatory coupling of external respiration to cellular respiration is inadequate to supply the muscles with the O_2 required to perform the exercise, the $\dot{V}O_2$ relative to work rate increase will be shallower than normal and the predicted peak $\dot{V}O_2$ will not be reached (Fig. 5.3B–E). Due to impaired O_2 flow to the working muscles, the peak $\dot{V}O_2$, *AT* and O_2 pulse are reduced (see cases in Chapter 10). The pattern of the decrease in $\Delta\dot{V}O_2/\Delta WR$ slope often reveals the cardiovascular pathophysiology limiting exercise (Fig. 5.3). From the abnormal patterns of the $\Delta\dot{V}O_2/\Delta WR$ slope, it is possible to distinguish left ventricular failure (Fig. 5.3D) from

Table 5.1

Disorders and Mechanisms Impairing Work Tolerance

Disorder	Pathophysiology	Primary Limitation
Obesity	Increased metabolic requirement; respiratory restriction	Decreased cardiorespiratory reserve
Peripheral arterial disease	Prevents normal vasodilatation; exercise hypertension	Impaired muscle O_2 supply; increased cardiac work
Heart failure	Reduced ability to increase cardiac output (stroke volume); ventilation–perfusion mismatching and possibly lung restriction when combined with obesity	Reduced tissue O_2 delivery; increased ventilatory requirement
Myocardial ischemia during exercise	Decrease in $\Delta\dot{V}O_2$ /ΔWR with sustained increase of $\Delta\dot{V}CO_2$ /ΔWR above *AT*; abrupt decrease in O_2 pulse; sharp increase in S2 of V-slope plot	Reduced exercise tolerance because of fatigue dyspnea or chest pain
Pulmonary vascular diseases	Limited cardiac output increase; increased ventilatory requirement relative to $\dot{V}CO_2$ and $\dot{V}O_2$	Impaired tissue O_2 delivery; increased ventilatory requirement
Airflow obstruction	Increased airway resistance; abnormal $\dot{V}A/\dot{Q}$	Reduced ventilatory capacity; increased ventilatory requirement
Restrictive lung disease	Limited ability to increase pulmonary blood flow; reduced lung distensibility; decreased efficiency of gas exchange; exercise-induced hypoxemia	Reduced tissue O_2 delivery; increased drive to breathe
Chest wall defect	Abnormal rib cage mechanics; respiratory muscle weakness	Reduced ability to breathe
Defects in hemoglobin content and quality	Reduced blood O_2 content; increased O_2 affinity for hemoglobin (left-shifted HbO_2 dissociation curve)	Impaired tissue O_2 delivery
Smoking	Increased carboxyhemoglobin; hypertension; increased airway resistance	Reduced tissue O_2; increased cardiac output demand; reduced ventilatory capacity
Metabolic acidosis	Reduced buffering capacity; low $PaCO_2$ set point	Increased ventilatory drive
Neuromuscular disease	Musculoskeletal coupling inefficiency	Reduced mechanical efficiency; pain
Glycolytic enzyme defect	Deficiency in carbohydrate substrate; inability to regenerate ATP by anaerobic metabolism	Muscle pain; reduced aerobic and anaerobic ATP regeneration
Electron transport defect	Inability to regenerate ATP aerobically	Low work rate metabolic acidosis
Anxiety	Nonphysiological breathing patterns	Shortness of breath
Poor effort or manipulated performance	Secondary gain; chaotic breathing: no or little metabolic acidosis at peak exercise	Self

AT, anaerobic threshold; ATP, adenosine triphosphate.

Table 5.2

Discriminating Measurements during Exercise in Obesity

High O_2 cost to perform external work
Upward displacement of $\dot{V}O_2$–work rate relationship
Peak $\dot{V}O_2$/body weight and *AT*/body weight values are low
Peak $\dot{V}O_2$/height and *AT*/height values are normal or high (with active lifestyle)
Normal to high O_2 pulse when determined from predicted weight
Low PaO_2 at rest that normalizes during exercise
Normal V_D/V_T
Failure to develop normal ventilatory compensation for metabolic acidosis
$\dot{V}E$ maintains a linear increase with work rate and $\dot{V}CO_2$

Peak $\dot{V}O_2$, highest O_2 uptake measured; *AT*, anaerobic threshold; V_D, physiological dead space; V_T, tidal volume.

exercise-induced myocardial ischemia in coronary artery disease (Fig. 5.3B), and these from pulmonary vascular disease (Fig. 5.3E) and peripheral arterial occlusive disease (Fig. 5.3C), particularly when associated with other physiological data as described below. The following describes the distinguishing features of the $\dot{V}O_2$ and $\dot{V}CO_2$ increases relative to the increases in work rate that characterize and distinguish these cardiovascular diagnoses.

Left Ventricular Failure

In left ventricular failure, the linearity of the $\dot{V}O_2$–work rate relationship is commonly abnormal and the $\Delta\dot{V}O_2/\Delta WR$ slope is reduced to a different extent in relationship to the rate at which work rate is increased.[2] The $\dot{V}O_2$ may increase normally as the work rate is increased at low levels, but $\dot{V}O_2$ gradually slows as the peak $\dot{V}O_2$ is approached. In this disorder, the subject's peak $\dot{V}O_2$ is clearly reduced. The nonlinear gradual slowing of the rate of rise in the slope of the $\dot{V}O_2$–work rate relationship in chronic heart failure is accompanied by a persistently steep $\dot{V}CO_2$–work rate slope (Fig. 5.3D). The increasing difference between the rise in $\dot{V}CO_2$ relative to that of $\dot{V}O_2$ reflects the CO_2 released from the bicarbonate (HCO_3) buffering of simultaneously generated lactic acid.[6,79]

Exercise-Induced Myocardial Ischemia in Developing Coronary Artery Disease

When the myocardial O_2 demand exceeds the myocardial O_2 supply due to myocardial ischemia, exercise-induced myocardial dyskinesis will be evident at the work and heart rate (HR) at which the myocardial wall becomes ischemic. Thus, $\dot{V}O_2$ increases normally with a $\Delta\dot{V}O_2/\Delta WR$ slope equal to 10 mL/min/W until the myocardium reaches its ischemic threshold. Then, the $\Delta\dot{V}O_2/\Delta WR$ slope abruptly decreases while the $\Delta\dot{V}CO_2/\Delta WR$ slope continues to rise relatively steeply (Fig. 5.3B; Cases 16–19 and 21 in Chapter 10).[7,13,34,70] The break in the $\Delta\dot{V}O_2/\Delta WR$ slope appears to occur before the electrocardiographic evidence of myocardial ischemia becomes evident, or without electrocardiogram (ECG) changes as reported by Chaudhry et al.[18] and in the cases of coronary artery disease referred to above.

Pulmonary Arterial Hypertension

While compensated at rest, patients with primary and secondary pulmonary vasculopathies have abnormally high pulmonary vascular resistance. This prevents the normal recruitment of pulmonary vascular bed and appropriate increase in pulmonary blood flow in response to exercise. Thus, like with left ventricular failure, $\dot{V}O_2$ does not increase at the normal rate of 10 mL/min/W. Instead, it gradually decreases below 10 mL/min/W, while $\dot{V}CO_2$ increases steeply (Fig. 5.3E). Thus, there are similarities in the decreased $\Delta\dot{V}O_2/\Delta WR$ slope to left ventricular failure. Differences are that patients with pulmonary arterial hypertension due to pulmonary vasculopathy often develop arterial hypoxemia, with or without a right-to-left shunt through a patent foramen ovale,[69] while patients with stable chronic left ventricular failure rarely develop hypoxemia during exercise.[80]

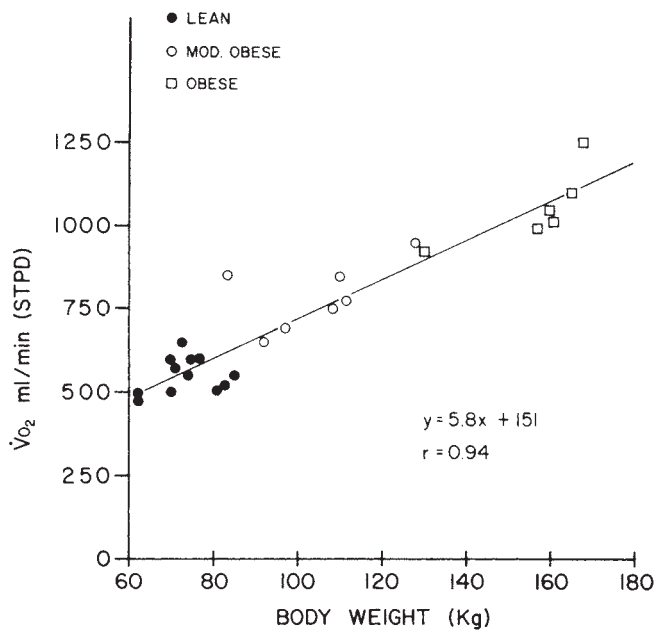

FIGURE 5.2. O_2 cost of performing unloaded cycling as related to body weight. (From Wasserman K, Whipp BJ. Exercise physiology in health and disease (state of the art). *Am Rev Respir Dis.* 1975;112:219–249, with permission.)

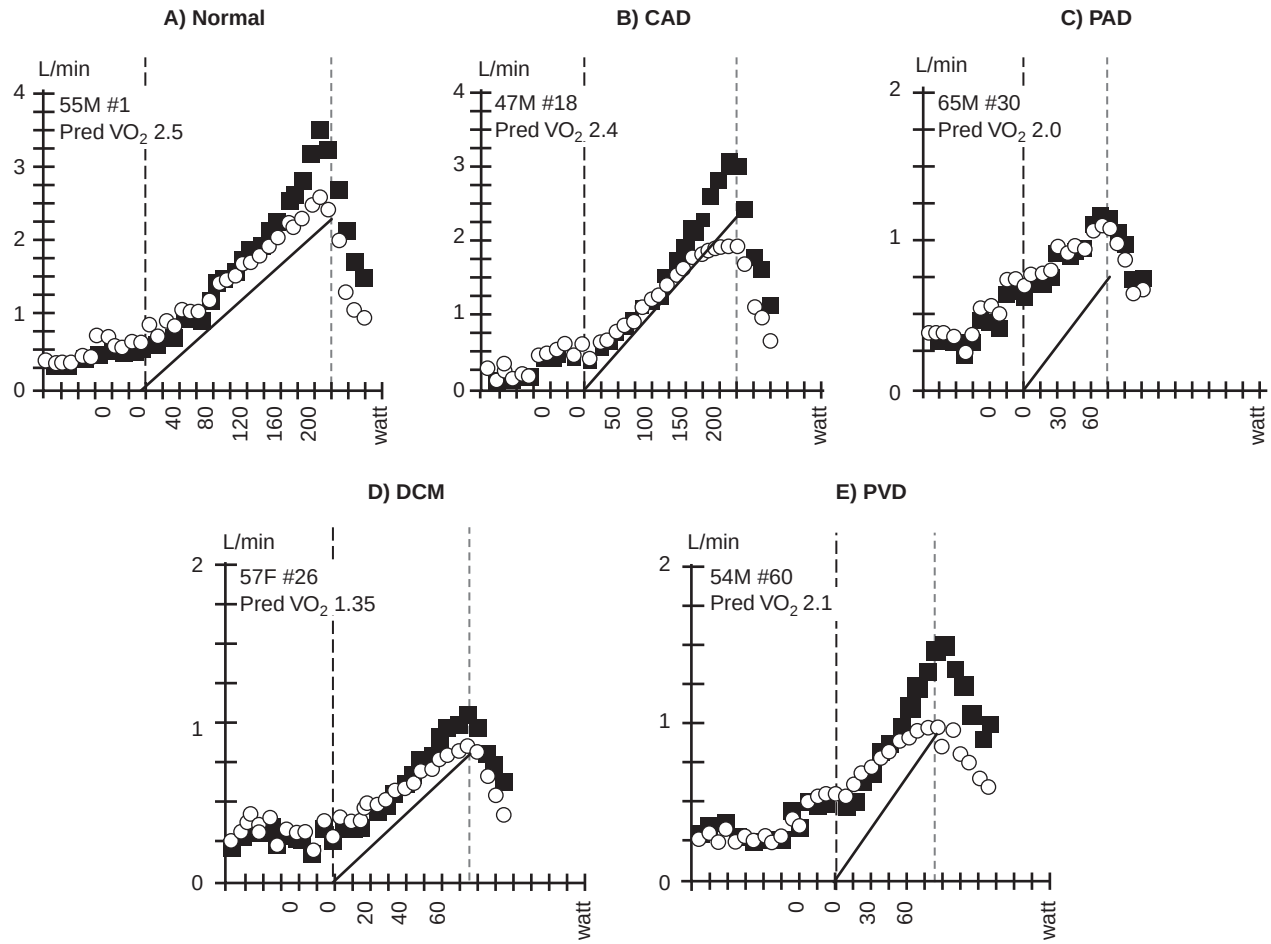

FIGURE 5.3. The pattern of increase in $\dot{V}O_2$ (*open circles*) and $\dot{V}CO_2$ (*solid boxes*) as related to increasing work rate (*diagonal line*) in four different cardiovascular pathophysiologies (**B–E**) as related to a normal response (**A**). The *diagonal line* shows the theoretical normal increase in $\dot{V}O_2$ relative to increase in work rate (WR) of 10 mL/min/W. **A:** A 55-year-old male whose peak $\dot{V}O_2$ and $\Delta\dot{V}CO_2/\Delta WR$ is normal (Case 1, Chapter 10). **B:** A 47-year-old male with coronary artery disease (CAD) (Case 18, Chapter 10) with reduced peak $\dot{V}O_2$ and myocardial dyskinesis demonstrable starting at about 150 watts. **C:** A 65-year-old male with peripheral artery disease (PAD) with reduced peak $\dot{V}O_2$, reduced $\Delta\dot{V}O_2/\Delta WR$, and reduced $\Delta\dot{V}CO_2/\Delta WR$ starting from unloaded cycling. **D:** A 57-year-old female with left ventricular failure (Case 26, Chapter 10) with reduced peak $\dot{V}O_2$, decreasing $\Delta\dot{V}O_2/\Delta WR$, and normally increasing $\Delta\dot{V}CO_2/\Delta WR$ starting from unloaded cycling. **E:** A 54-year-old male with a pulmonary vascular disorder (PVD) (Case 60, Chapter 10) with reduced peak $\dot{V}O_2$, reduced $\Delta\dot{V}O_2/\Delta WR$ and normally increasing $\Delta\dot{V}CO_2/\Delta WR$ starting from unloaded cycling. DCM, dilated cardiomyopathy.

Peripheral Arterial Disease

In peripheral arterial occlusive disease, the fixed stenosis of major arteries branching from central parent arteries prevents the normal increase in blood flow to exercising muscles. Therefore, with lower extremity exercise, $\dot{V}O_2$ increases linearly but relatively shallowly, as shown in Figure 5.3C. In contrast to other cardiovascular disorders, the slope of $\dot{V}CO_2$ relative to work rate increase is also relatively shallow, which is a result of the low fraction of the cardiac output flowing through the ischemic muscle. Thus, the reduced $\Delta\dot{V}O_2/\Delta WR$ slope increases in a linear but reduced rate. In contrast to other disorders of the central circulation, the $\Delta\dot{V}CO_2/\Delta WR$ slope is pathologically shallow like the $\Delta\dot{V}O_2/\Delta WR$ slope.

Why Do Cardiovascular Disorders Impair Gas Transport?

Because gas transport is the major and most immediate function of the cardiovascular system, cardiac dysfunction of all five primary types of heart disease (i.e., rate response, coronary artery, cardiomyopathic, valvular, and congenital) will cause changes in the pattern of $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$, $PETCO_2$, $PETO_2$, HR, and blood pressure responses to exercise and their relationships.

In nearly all heart defects (with the exception of heart block), the increase in HR as a function of $\dot{V}O_2$ is steeper than normal. This reflects the increased dependence on HR and arteriovenous O_2 extraction to increase the O_2 transport, which is essential for exercise. Although the

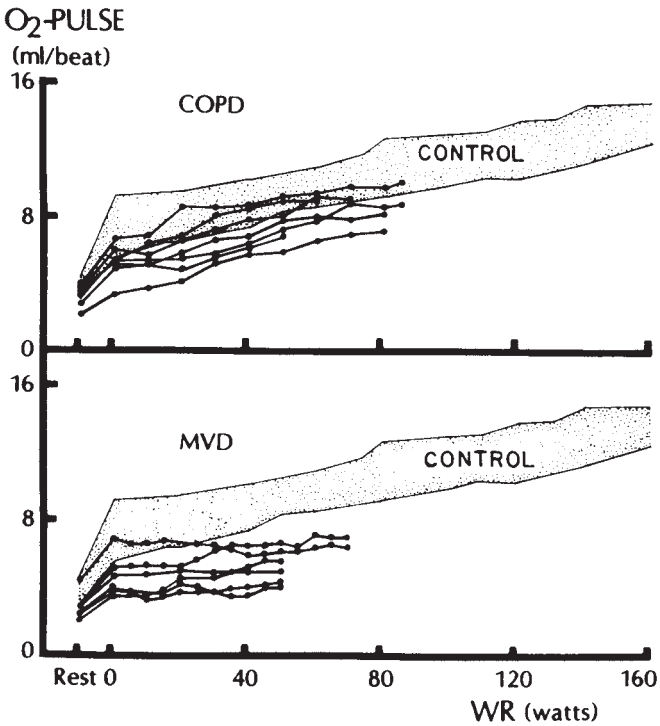

FIGURE 5.4. O_2-pulse response to incremental exercise in patients with chronic obstructive pulmonary disease (COPD) **(upper panel)** and mitral valve disease (MVD) **(lower panel)** compared with the range of values of a control group *(stippled area)*. (Modified from Nery LE, Wasserman K, French W, et al. Contrasting cardiovascular and respiratory responses to exercise in mitral valve and chronic obstructive pulmonary diseases. *Chest.* 1983;83:446–453.)

HR–$\dot{V}O_2$ relationship is usually relatively steep in heart disease because stroke volume is reduced, exceptions occur when the HR response to exercise may be inappropriately low, such as in patients taking high doses of β-adrenergic blocking drugs, patients with chronotropic incompetence, and patients with heart block.

Because of the relatively low cardiac output response, mixed venous oxygen reaches its lowest value, and the arterial–mixed venous oxygen difference $[C(a-\bar{v})O_2]$ its highest value at a low work rate.[53,82] Consequently, the O_2 pulse $[C(a-\bar{v})O_2 \times SV]$ reaches a constant value that is abnormally low and occurs at an unusually low work rate compared to normal (Fig. 5.4). The increase in $\dot{V}O_2$ as WR increases commonly becomes smaller near the maximum work rate (see Fig. 5.3), reflecting a decrease in energy from aerobic metabolism, presumably because of impaired O_2 transport[77] or utilization.[66]

A number of studies have shown that patients with chronic left ventricular failure develop mismatching of ventilation relative to pulmonary perfusion, particularly of the high $\dot{V}A/\dot{Q}$ type. This results in an increased V_D/V_T and a further increase in the breathing requirement to maintain blood pH homeostasis.[37,38,49,58,68,80] The need to maintain pH homeostasis in the presence of the increase in V_D/V_T is the major factor, along with the increase in $\dot{V}CO_2$ in response to developing lactic acidosis, accounting for the increased ventilatory response to exercise,[80] and likely contributes to the symptom of dyspnea in patients with chronic left ventricular failure.

Constant work rate tests may be helpful for evaluating the cardiovascular response to specific levels of exercise in heart diseases.[39,44] If the work rate is above the lactic acidosis threshold, $\dot{V}O_2$ will not reach a steady state by 3 minutes. The magnitude of the increase in $\dot{V}O_2$ between 3 and 6 minutes $[\Delta\dot{V}O_2\ (6-3)]$ is correlated with the exercise lactic acidosis (see Figs. 4.27 and 4.30).

HEART DISEASES

Coronary Artery Disease

Although mild coronary artery disease may be difficult to detect, simultaneous gas exchange measurements with the ECG improve the diagnostic capabilities of an exercise stress test (Table 5.3). Coronary artery disease will usually cause the peak $\dot{V}O_2$ to be reduced. Patients with coronary artery disease may or may not experience chest pain. When the exercise-induced increase in myocardial oxygen requirement is not met by the myocardial oxygen supply, myocardial ischemia may result with characteristic ECG changes. These might be preceded by the characteristic gas exchange abnormalities of exercise-induced myocardial ischemia (Fig. 5.3B).

The $\dot{V}O_2/\Delta WR$ ratio is normal at low work rates of an incremental exercise test, but abruptly decreases when myocardial ischemia fails to generate sufficient adenosine triphosphate (ATP) to maintain myocardial contraction and stroke volume (myocardial dyskinesis). The ECG usually becomes abnormal, whether or not chest pain develops, when or after $\dot{V}O_2/\Delta WR$ starts to decrease.[7,34] Despite a decrease in $\Delta\dot{V}O_2/\Delta WR$ because of myocardial dyskinesis due to myocardial ischemia, $\dot{V}CO_2$ continues to increase steeply, creating a large disparity between the increase in $\dot{V}CO_2$ and $\dot{V}O_2$. With myocardial ischemia, HR usually increases more steeply as a function of

Table 5.3

Discriminating Measurements during Exercise in Peripheral Arterial Disease

Low $\dot{V}O_2/\Delta WR$; low $\Delta\dot{V}CO_2/\Delta WR$
Low maximum $\dot{V}O_2$
Low *AT*
Leg pain
Exercise-induced hypertension

$\Delta\dot{V}O_2/\Delta WR$, increase in $\dot{V}O_2$ relative to increase in work rate; *AT*, anaerobic threshold.

$\dot{V}O_2$, developing a curvilinear HR versus $\dot{V}O_2$ relationship rather than the normal linear relationship.

The O_2 pulse fails to increase to its normal predicted value when myocardial ischemia develops, often becoming flat or decreasing despite increasing work rate. The decreased O_2 pulse is likely due to a decrease in stroke volume secondary to myocardial dyskinesis while $C(a - \bar{v})O_2$ is simultaneously increasing. These simultaneous changes often maintain a constant, albeit reduced, O_2 pulse during increasing work rate in patients with heart failure (Fig. 5.4) and coronary artery disease (see Cases 16–21 in Chapter 10).

In normal persons, the O_2 pulse decreases immediately after exercise. However, a paradoxical increase in O_2 pulse commonly occurs in patients who develop myocardial ischemia or heart failure in response to exercise. This paradoxical increase in O_2 pulse may be due to an immediate increase in stroke volume in these patients because of the abrupt decrease in left ventricular afterload when exercise stops.[40]

Metabolic acidosis usually develops because of impaired O_2 transport resulting from the failure to increase cardiac output commensurate with the increasing work rate when a significant portion of the left ventricle stops contracting normally. How much metabolic acidosis develops depends on the number of minutes the subject exercises after myocardial ischemia develops and the level of exercise performed.

In patients with coronary artery disease, the breathing reserve is normal or high because the subject is forced to stop exercise from symptoms at a relatively low metabolic rate. The ventilatory equivalents are normal, reflecting relatively uniform ventilation–perfusion relationships, in contrast to the nonuniform ventilation–perfusion relationships observed in patients with chronic stable heart failure.

Myopathic Heart Disease

Because patients with ischemic or idiopathic dilated cardiomyopathies have difficulty in transporting oxygen to the skeletal muscles during exercise, the increase in $\dot{V}O_2$ relative to the increase in work rate is slower than normal (Table 5.4). This slowing, however, is not abrupt, in contrast to the slowing of $\dot{V}O_2$ increase relative to work rate seen in patients who develop acute myocardial ischemia during exercise. The failure to transport O_2 at the rate needed to regenerate the ATP needed for muscular contraction makes it impossible to sustain muscular contraction; consequently, the muscles fatigue and the subject must stop.

The peak $\dot{V}O_2$ is reduced consequent to the reduced peak cardiac output response to exercise. The *AT* is also commonly reduced.[27,81] The peak O_2 pulse is low because of the reduced stroke volume. The HR increase is commonly steep relative to the increase in $\dot{V}O_2$, except on high doses of β-adrenergic blocking or other negative chronotropic drugs such as digitalis or amiodarone. The maximal HR may be reduced in patients with heart failure because the cardiomyopathy is accompanied by chronotropic incompetence, heavy β-adrenergic blockade, or early exercise fatigue.

Table 5.4

Discriminating Gas Exchange Measurements during Exercise in Coronary Artery Disease

$\Delta\dot{V}O_2/\Delta WR$ normal at low work rates, but may change to more shallow slope above *AT*
Reduced maximal O_2 pulse
Heart rate–$\dot{V}O_2$ relationship is nonlinear, becoming abnormally steep as peak $\dot{V}O_2$ is approached
High breathing reserve
Metabolic acidosis at end exercise
Occasional immediate post-exercise increase in O_2 pulse

$\Delta\dot{V}O_2/\Delta WR$, increase in $\dot{V}O_2$ relative to increase in work rate; *AT*, anaerobic threshold.

Because of the relatively low cardiac output response to exercise, mixed venous oxygen reaches its lowest value, and $C(a - \bar{v})O_2$ reaches its highest value, at a low work rate.[82] Consequently, the O_2 pulse ($[C(a - \bar{v})O_2] \times SV$) reaches a constant value that is low and that occurs at an unusually low work rate compared with normal (Fig. 5.4). As described earlier, $\Delta\dot{V}O_2/\Delta WR$ is often reduced as the maximum work rate is approached. This can be viewed as a reflection of an increased contribution of energy from anaerobic metabolism, presumably because of impaired O_2 transport[77] or utilization.[67]

Patients with heart failure have a high ventilatory requirement relative to the metabolic rate of the subject.[20,27,37,49] In fact, the ventilatory requirement relative to CO_2 output has been used as a prognosticator of survival.[20,37,41] Three factors contribute to this high ventilatory requirement. Most importantly, patients with chronic heart failure develop mismatching of ventilation relative to pulmonary perfusion, particularly of the high $\dot{V}A/\dot{Q}$ type, resulting in an increased V_D/V_T. The latter correlates with the degree of functional impairment in exercise performance (Fig. 5.5). This reduced gas exchange efficiency is a major factor accounting for the increased ventilatory drive in heart failure. Second, a metabolic acidosis occurs at lower work rates in patients with heart failure compared with normal.[65,80,83] The increase in CO_2 produced at low work rates, because of the buffering of lactic acid by HCO_3^-, increases the acid load to the ventilatory system. These factors combine to increase the breathing requirement to maintain arterial H^+ homeostasis in response to exercise,[80] and likely contribute to the symptom of dyspnea in patients with chronic heart failure.

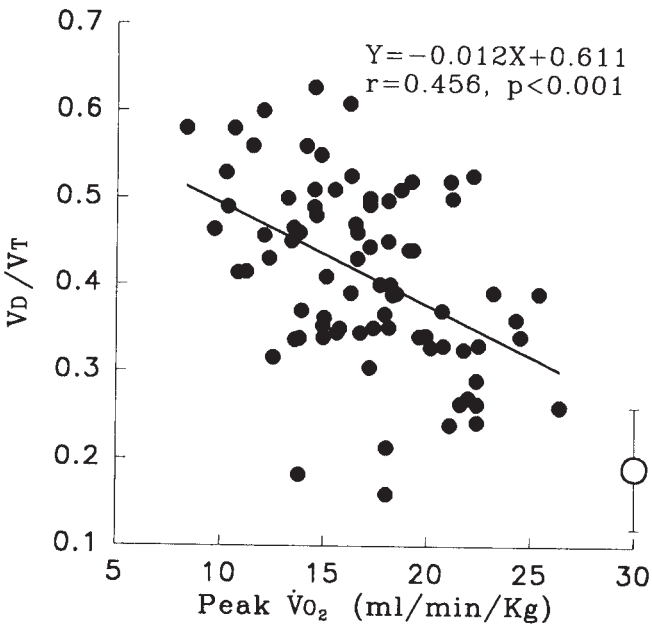

FIGURE 5.5. Ratio of physiological dead space to tidal volume (V_D/V_T) as a function of peak $\dot{V}O_2$ on a cycle ergometer in 78 patients with chronic stable heart failure. The open circle on the right is the mean V_D/V_T ± standard deviation for normal subjects. (From Wasserman K, Zhang YY, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. *Circulation*. 1997;96:2221–2227, with permission.)

A regular oscillatory pattern of breathing in which $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, and related variables increase and decrease with a period of approximately 45 to 90 seconds is observed in some patients with more severe chronic heart failure.[42,84] This oscillatory pattern in gas exchange is more marked at lower work rates and tends to diminish and even to disappear as the subject nears the maximum work rate. During this oscillatory breathing, the phasic changes in $\dot{V}O_2$ lead $\dot{V}CO_2$ and, more particularly, $\dot{V}E$.[8] This suggests that flow through the pulmonary circulation is oscillating.[8,84] Thus, oscillatory changes in arterial blood gases and pH could be inducing the oscillating gas exchange patterns.

These oscillatory changes in pulmonary blood flow likely reflect the behavior of the failing heart. Cardiac output changes rhythmically in response to the rhythmic changes in left ventricular after-load secondary to changes in systemic arterial resistance originating from the vasomotor center (Traube-Hering waves). This behavior contrasts with that of the normal heart in which the forward output adjusts to changes in the venous return (preload) and is less dependent on changes in systemic arterial resistance (afterload) than in someone with a failing heart. The presence of periodic breathing during exercise is associated with a poor prognosis in heart failure.[24] About 20% of heart failure patients have atrial fibrillation. The presence of atrial fibrillation is associated with a lower exercise performance and lower peak $\dot{V}O_2$.[1]

Valvular Heart Disease

Because the stroke volume is reduced in patients with valvular heart disease, the increase in $\dot{V}O_2$ relative to increase in work rate is usually reduced (i.e., low $\Delta\dot{V}O_2/\Delta WR$; Table 5.5). Both the *AT* and the peak $\dot{V}O_2$ are reduced. The O_2 pulse is reduced and reaches a plateau value at a relatively low work rate (Fig. 5.4). HR increases steeply relative to $\dot{V}O_2$, with the maximal HR achieved at a relatively low work rate.

Congenital Heart Disease

Constant work-rate tests are of particular value in patients with congenital heart disease (Table 5.6). Because the increases in $\dot{V}O_2$ and $\dot{V}CO_2$ are determined by the increase in flow of O_2-desaturated, CO_2-rich blood through the pulmonary circulation, the pattern of increase in blood flow through the lungs can be measured from the O_2 uptake and CO_2 output kinetics. Thus, patients with pulmonary artery outflow obstruction[61] or patients with an increase in right-to-left shunt may fail to demonstrate a normal increase in blood flow at the start of exercise, resulting in a reduced or absent phase I increase in $\dot{V}O_2$ and $\dot{V}CO_2$.[63] Phase II kinetics are also inappropriately slow, and the magnitude of phase II becomes a relatively

Table 5.5

Discriminating Gas Exchange Measurements during Exercise in Chronic Heart Failure

$\dot{V}O_2$ increase with WR may gradually slow near peak $\dot{V}O_2$
Reduced peak $\dot{V}O_2$
Reduced *AT*
Reduced maximal O_2 pulse
Steep HR–$\dot{V}O_2$ relationship with low maximal HR
Possible development of oscillatory breathing and gas exchange pattern of 45- to 90-second periods at low WR; oscillatory pattern is less evident as peak WR is reached
O_2 pulse increases paradoxically immediately after exercise
Slow $\dot{V}O_2$ kinetics and high $\Delta\dot{V}O_2$ (6 – 3) above *AT* during constant work rate test
Increased V_D/V_T, $\dot{V}E/\dot{V}CO_2$ at *AT*, and slope of $\dot{V}E$ versus $\dot{V}CO_2$ are related to degree of severity

AT, anaerobic threshold; HR, heart rate; $\Delta\dot{V}O_2$ (6 – 3), difference between $\dot{V}O_2$ at 6 and 3 minutes during constant work rate exercise; V_D/V_T, physiological dead space/tidal volume ratio; $\dot{V}E$, minute ventilation; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for CO_2.

Table 5.6

Discriminating Gas Exchange Measurements in Valvular Heart Disease

- $\Delta\dot{V}O_2/\Delta WR$ commonly low
- Low peak $\dot{V}O_2$
- Low *AT*
- Low and unchanging O_2 pulse
- Steep linear increase in HR–$\dot{V}O_2$ relationship
- Slow $\dot{V}O_2$ kinetics and high $\Delta\dot{V}O_2$ (6 – 3) at relatively low constant work rate test

AT, anaerobic threshold; HR, heart rate; $\Delta\dot{V}O_2$ (6 – 3), difference between $\dot{V}O_2$ at 6 and 3 minutes during constant work rate exercise; VD/VT, physiological dead space/tidal volume ratio; $\dot{V}E$, minute ventilation; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for CO_2.

large portion of the total O_2 requirement at low work rates.[73] A slowly rising $\dot{V}O_2$ is also evident at relatively low work rates during phase III. Thus, $\Delta\dot{V}O_2$ between 3 and 6 minutes of exercise is increased, indicating that lactate is increasing in response to the exercise. As in other cardiovascular disorders, the peak $\dot{V}O_2$ and *AT* are reduced.

A markedly elevated ventilatory response is noted at the start of exercise in patients with cyanotic congenital heart disease.[62] In this disorder, the blood flowing through the lungs is hyperventilated to compensate for the blood that bypasses the lungs and enters the left side of the circulation through the right-to-left shunt. Hyperventilation of the blood passing through the lungs results in an immediate decrease in $PETCO_2$, an increase in $PETO_2$, an increase in the respiratory exchange ratio (R), and usually an increase in $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ at the start of exercise; this decrease is sustained until the start of recovery. $PaCO_2$ and pH remain relatively unchanged in patients with a right-to-left shunt, whereas the PaO_2 decreases.[62] The relatively unchanged acid–base status suggests that the respiratory control mechanism is sensitive to the regulation of arterial $[H^+]$ and is not greatly influenced by the high pulmonary artery pressures in this population of patients. In congenital heart diseases accompanied by a left-to-right shunt—for example, a patent ductus arteriosus (Case 34 in Chapter 10)—or in dialysis patients with an a–v fistula, peak $\dot{V}O_2$, and *AT* are reduced because of the diversion of a sizable part of the cardiac output through the low-resistance shunt (Table 5.6).

PULMONARY VASCULAR DISEASES

Causes of Increased Ventilation

Disorders of the pulmonary circulation, such as idiopathic pulmonary vasculopathy (idiopathic or familial pulmonary arterial hypertension), pulmonary emboli, and other causes of pulmonary vasculopathy[52] have hypoperfusion to ventilated alveoli, particularly during exercise (Table 5.7). Consequently, alveoli with nonoccluded capillaries must accept a greater than normal perfusion and must be ventilated to a proportionately greater degree than normal to remove the metabolic CO_2 and to maintain $PaCO_2$, PaO_2, and pH at appropriate levels. The overventilation of the poorly perfused alveoli is wasted (alveolar dead space). Because of the increase in physiological dead space ventilation, minute ventilation is increased in patients with pulmonary vascular diseases at rest, and to a greater degree during exercise. The increased dead space ventilation results in a high VD/VT and a persistently positive $P(a-ET)CO_2$ during exercise. $PETCO_2$ is reduced in pulmonary hypertension for two reasons: (1) hypoperfusion of ventilated acini and (2) opening of the foramen ovale, causing a right-to-left shunt during exercise that may not be present at rest. If a right-to-left shunt develops during exercise, VD/VT and $P(a-ET)CO_2$ will increase further as the size of the shunt increases.

An additional cause of increased ventilatory drive during exercise in many patients with pulmonary vascular occlusive disease is arterial hypoxemia, which gets worse during exercise. The decrease in PaO_2 stimulates the carotid bodies, which are the chemoreceptors that stimulate ventilation in the presence of arterial hypoxemia.[21]

Table 5.7

Discriminating Gas Exchange Measurements during Exercise in Congenital Heart Disease

- Right-to-left shunt
  - Low peak $\dot{V}O_2$
  - Low *AT*
  - Increased $\dot{V}E/\dot{V}CO_2$ at *AT*
  - Phase I $\dot{V}O_2$ reduced when accompanied by increased pulmonary vascular or valvular resistance
  - Slow $\dot{V}O_2$ kinetics and high $\Delta\dot{V}O_2$ (6 – 3) during constant work rate test
  - Immediate hyperpnea and decrease in $PETCO_2$ in cyanotic type; magnitude of increase in $\dot{V}E$ and decrease in $PETCO_2$ related to size of right-to-left shunt
  - Worsening arterial hypoxemia with exercise
- Left-to-right shunt
  - Low peak $\dot{V}O_2$
  - Low *AT*
  - Normal $\dot{V}E/\dot{V}CO_2$ at *AT*
  - Normal arterial oxygenation during exercise

AT, anaerobic threshold; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for CO_2; $\Delta\dot{V}O_2$ (6 – 3), difference between $\dot{V}O_2$ at 6 and 3 minutes during constant work rate exercise; $\dot{V}E$, minute ventilation.

Causes of Exercise Arterial Hypoxemia

Pa_{O_2} may be near normal at rest but there may be striking arterial oxyhemoglobin desaturation during exercise. Several mechanisms may play a role. First, the time available for diffusion equilibrium of O_2, already shortened at rest by the reduced size of the functional capillary bed, is further shortened by the exercise-induced increase in pulmonary blood flow. In the normal capillary bed, the red cell residence time is about 0.8 second at rest.[22] Despite increasing cardiac output as much as fourfold at maximal exercise in the fit normal subject, the red cell residence time is still above 0.3 second (the time required for O_2 equilibration between capillary and alveolar space in a normal acinus) because of recruitment of pulmonary capillaries (approximately doubling the resting capillary blood volume). However, in the presence of pulmonary vascular occlusive disease, the functional capillary bed is destroyed and the capillary bed reserved for recruitment to perform exercise is already recruited at rest. Thus, red cell transit times through the pulmonary capillaries are shortened during exercise. Consequently, the desaturated red cell arriving from the systemic venous circulation may not remain in the pulmonary capillary bed long enough for diffusion equilibrium of O_2 between the alveolar gas and red cell to occur, especially in response to exercise. High-$\dot{V}_A/\dot{Q}$ lung units predominate in chronic pulmonary vascular occlusive disease in patients without airway disease.

Another cause of hypoxemia during exercise in patients with increased pulmonary vascular resistance is the development of a right-to-left shunt resulting from the opening of a potentially patent foramen ovale. Approximately 35% of the normal population is thought to have an "unsealed" foramen ovale. In the healthy subject, this is of no importance because left atrial pressure is normally higher than right atrial pressure and blood does not shunt in either direction. However, if pulmonary vascular resistance is increased so that the right ventricle cannot pump the venous return into the pulmonary circulation as fast as it is delivered (right ventricular failure), right ventricular end-diastolic pressure and, therefore, right atrial pressure will increase. If the right atrial pressure exceeds that of the left atrium, some of the right atrial flow will pass through the unsealed foramen ovale, creating a right-to-left shunt. This can cause marked exercise hypoxemia and may be only evident during exercise.[69] The development of a right-to-left shunt can easily be identified by the abrupt increase in P_{ETO_2}, abrupt decrease in P_{ETCO_2}, and a sustained increase in R to a value of approximately 1.0, accompanied by increases in $\dot{V}_E/\dot{V}_{O_2}$and $\dot{V}_E/\dot{V}_{CO_2}$ at the start of exercise. Repeating the exercise test while the subject breathes 100% oxygen clearly confirms and quantifies a right-to-left shunt. If the shunt develops during O_2 breathing, the arterial P_{O_2} should decrease well below that predicted for normal subjects (>550 mm Hg). The Pa_{O_2} will decrease approximately 100 mm Hg for every 3% to 5% of cardiac output passing through the right-to-left shunt.

Effect on Systemic Hemodynamics

Pulmonary vascular occlusive diseases cause a hemodynamic stenosis in the central circulation, making it difficult for the right ventricle to deliver blood to the left atrium at a rate sufficient to meet the increased cardiac output needed for exercise. Because the cardiac output increase in response to exercise is reduced, the *AT* and peak $\dot{V}_{O_2}$ and O_2 pulse are reduced in patients with pulmonary vascular disease, similar to that seen in patients with left heart failure. In both conditions, the V_D/V_T and $\dot{V}_E/\dot{V}_{CO_2}$ at the *AT* and the $\dot{V}_E$ versus $\dot{V}_{CO_2}$ slope are increased. However, the arterial oxyhemoglobin desaturation helps distinguish the pathophysiology of pulmonary vascular occlusive disease from chronic left ventricular failure. Oxygenation is normal in patients with left ventricular failure, presumably because of the slow flow through the pulmonary capillary bed. In contrast, systemic arterial blood is often desaturated in patients with pulmonary vascular occlusive disease. As described earlier, the pulmonary capillary blood volume is reduced in the latter condition. Thus, the transit time of red cells through the pulmonary capillary bed is abnormally rapid, shortening the time available for O_2 to equilibrate between the alveolar gas and the red cell. In addition, right to left shunting through a patent foramen ovale may also occur, causing major systemic arterial oxyhemoglobin desaturation.

Because the heart commonly enlarges in patients with left ventricular failure, the vital capacity tends to be reduced more than that observed with pulmonary vascular diseases. Thus, a decrease in vital capacity, normal arterial oxygenation and increasing, rather than decreasing, P_{ETCO_2} during exercise might differentiate left ventricular failure from primary pulmonary vascular occlusive disease in patients with steep ventilatory responses to exercise.

PERIPHERAL ARTERIAL DISEASES

Because of atherosclerotic changes that reduce the internal diameter of the conducting arteries to the limbs, peripheral arterial diseases prevent the increase in blood flow needed to meet the increased metabolic demand of exercise (Table 5.8). Thus, O_2 flow to muscles fails to increase sufficiently to satisfy the O_2 requirement for performing exercise. The inability to supply sufficient O_2 to the exercising muscles to meet the O_2 requirement is reflected in a reduced $\Delta\dot{V}_{O_2}/\Delta WR$ ratio at low work levels (Fig. 5.3C). Although a compensatory increase in mitochondrial number in the ischemic muscle may

Table 5.8

Gas Exchange Abnormalities during Exercise in Diseases of the Pulmonary Circulation

High $\dot{V}_E$ at submaximal work rates
High V_D/V_T
Positive $P(a-ET)CO_2$ during exercise
PaO_2 decreases as WR is increased
$P(A-a)O_2$ increases with increasing WR
Low peak $\dot{V}O_2$
Low *AT*
$\Delta\dot{V}O_2/\Delta WR$ more shallow toward maximum WR
Low O_2 pulse

$\dot{V}_E$, minute ventilation; V_D/V_T, physiologic dead space/tidal volume ratio; $P(a-ET)CO_2$, arterial-end tidal PCO_2 difference; $P(A-a)O_2$, alveolar-arterial PO_2 difference; $\Delta\dot{V}O_2/\Delta WR$, increase in $\dot{V}O_2$ relative to increase in work rate.

Table 5.9

Discriminating Measurements during Exercise in Patients with Obstructive Lung Disease

Low peak $\dot{V}O_2$
Low breathing reserve
High heart rate reserve
High V_D/V_T
Increased $P(a-ET)CO_2$ during exercise
Usually high $P(A-a)O_2$
Increased O_2 cost of work
Failure to develop respiratory compensation for exercise metabolic acidosis
Decreased IC with exercise (air trapping)
Abnormal expiratory flow pattern

V_D/V_T, physiological dead space/tidal volume ratio; $P(a-ET)CO_2$, arterial-end tidal PCO_2 difference; $P(A-a)O_2$, alveolar-arterial PO_2 difference; IC, inspiratory capacity.

occur with time, the improved O_2 extraction that this mechanism portends is inadequate to make up for the deficiency in O_2 flow.[16] Consequently, the ischemic muscles produce lactic acid at relatively low work rates, with subsequent leg pain and fatigue. Because of slow blood flow through the ischemic leg, relatively little of the lactic acid and the CO_2 released from HCO_3^- buffering of new lactic acid produced in the muscle are readily seen in the lung gas exchange. Thus, $\Delta\dot{V}CO_2/\Delta WR$ may, like $\Delta\dot{V}O_2/\Delta WR$, be relatively shallow.

With peripheral arterial disease, the maximum $\dot{V}O_2$ and the lactic acidosis threshold are reduced, although the latter may not be detectable because lactate may enter the central circulation very slowly as a result of reduced muscle perfusion. Thus, the lactic acidosis of the ischemic muscles may not always be obvious from gas exchange.

Patients with peripheral arterial disease have systemic arterial hypertension at the low work rates. The HR at maximum exercise is usually relatively low because the patient stops exercise from claudication at a work rate too low to provide maximal HR stimulation.

VENTILATORY DISORDERS

Obstructive Lung Diseases

Patients with chronic obstructive pulmonary diseases (COPD), including emphysema, chronic bronchitis, bronchial asthma, and mixtures of these disease entities, are usually limited during exercise by dyspnea or fatigue (Table 5.9). Dyspnea generally results from difficulty in achieving the ventilation and, possibly, the O_2 cost of ventilation needed to eliminate the additional CO_2 generated during exercise at the level of $PaCO_2$ regulated by the patient (the patient's PCO_2 set point). Also, many of these patients are highly sedentary and develop a lactic acidosis at a relatively low work rate (Table 5.10). The added CO_2 load resulting from the HCO_3^- buffering of lactic acid and the H^+ provide additional chemical stimuli to breathe to an inefficient gas-exchanging lung.

Ventilatory Capacity–Ventilatory Requirement Imbalance

Figure 5.6 conceptualizes the pathophysiologic features leading to dyspnea in patients with COPD. The two major contributing factors are the decreased ventilatory capacity and the increased ventilatory requirement. In emphysema, the decreased ventilatory capacity is due to increased airflow obstruction combined with reduced lung elastic recoil, whereas in chronic bronchitis and asthma, the decreased ventilatory capacity is due to increased airway resistance.

The increased ventilatory requirement in patients with COPD is primarily due to inefficient ventilation of the lungs consequent to the mismatching of ventilation to perfusion; that is, certain regions of the lungs are hypoventilated, whereas others are hyperventilated. This has the effect of increasing the fraction of the breath that is wasted (increased V_D/V_T), thereby requiring an increased ventilation to eliminate the CO_2 produced by the patient to maintain the arterial PCO_2 at its apparent set point.

As shown in Figure 5.7, ambulatory patients with stable obstructive lung disease regulate $PaCO_2$ at a reasonably constant level despite increasing work rates. However, ventilatory compensation for the exercise-induced lactic acidosis rarely occurs in these patients (see cases of patients with COPD in Chapter 10). With severe

Table 5.10

Effect of Airway Obstruction Due to Emphysema on Average Blood Lactate Concentration, Minute Ventilation, and Work Rate at an O_2 Consumption of Approximately 1.0 L/min

FEV_1 (L)	$\dot{V}O_2$ (L/min, STPD)	WR (watts)	$\dot{V}E$ (L/min, BTPS)	$\dot{V}E/\dot{V}O_2$	La^- (mmol/L)	$La^-/\dot{V}O_2$
1.02	0.90	35	35	39	3.03	3.37[a]
1.80	1.05	34	36	34	2.95	2.80[b]
Normal	~1.0	50	25	25	<1.0	1.0[c]

[a]Mean data from Cooper CB, Daly JA, Burns MR, et al. Lactic acidosis contributes to the production of dyspnea in chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1991;143:A80.
[b]Mean data from Casaburi R, Patessio A, Ioli F, et al. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis.* 1991;143:9–18.
[c]Mean data from Chapter 2.
FEV_1, forced expiratory volume in 1 second; WR, work rate; $\dot{V}E$, minute ventilation; La^-, blood lactate concentration; STPD, standard temperature and pressure, dry; BTPS, body temperature, ambient pressure, saturated.

airway obstruction, $PaCO_2$ may increase during exercise because of the increased work of breathing, thereby worsening the exercise acidosis.[50] Hypoxemia in COPD results from underventilation of perfused lung units. Despite increasing ventilatory drive through the carotid body chemoreceptors,[21] the hypoxic stimulus is insufficient to induce an increased respiratory drive that decreases $PaCO_2$ in patients with COPD. Although regulation of PaO_2 is less precise than $PaCO_2$ in these patients (Fig. 5.8), PaO_2 usually does not fall to extremely low levels, even at the patient's maximum work rate.

The $P(A-a)O_2$ is usually increased as a consequence of the perfusion of relatively poorly ventilated airspaces. The increase in $P(A-a)O_2$ is usually not systematic with increasing work rate, as is common in patients with primary pulmonary vascular diseases or pulmonary fibrosis. $P(a-ET)CO_2$ is also increased, reflecting overventilation relative to perfusion. Thus, $P(a-ET)CO_2$ remains relatively constant and elevated as work rate is increased, rather than decreasing and becoming negative as in normal subjects (see Chapter 7). Because patients with COPD ventilate the fast time constant lung units predominantly, the mixed expired CO_2 is low relative to the end-tidal CO_2, which is derived predominantly from the slow, low $\dot{V}/\dot{Q}$ lung units. Thus, the ratio of mixed expired to end-tidal PCO_2 has been shown to distinguish between uneven $\dot{V}/\dot{Q}$ due to uneven perfusion from uneven ventilation.[30]

Although one may predict that the O_2 cost of breathing will be increased in patients with COPD, this has been difficult to demonstrate. That these patients do have an increased metabolic cost becomes evident, however, when one examines the external work that can be performed

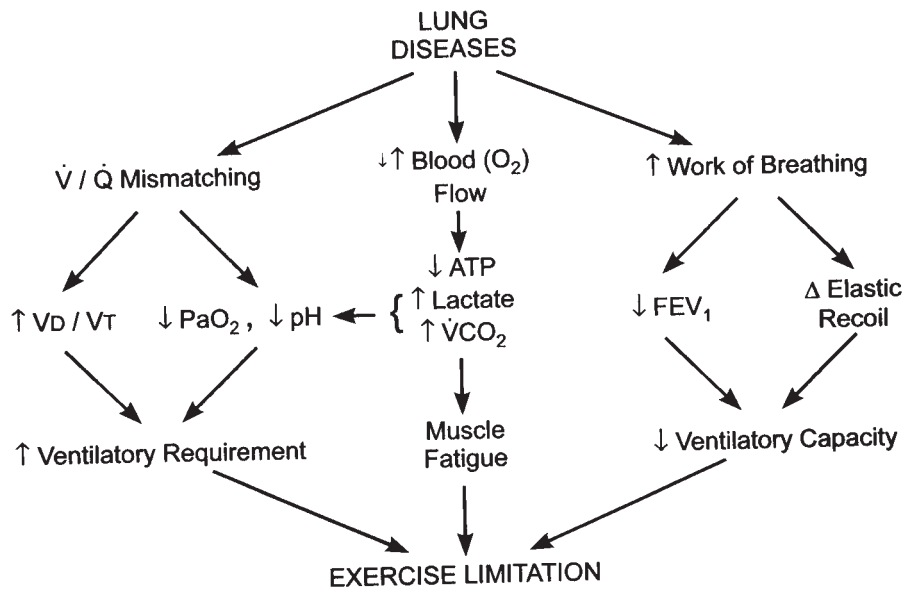

FIGURE 5.6. Factors that play a role in exercise limitation and dyspnea in patients with chronic obstructive pulmonary disease (COPD). These patients have both an increase in ventilatory requirement to perform exercise and a reduction in ventilatory capacity. See text for a detailed discussion of each of the factors shown. $\dot{V}/\dot{Q}$, ventilation–perfusion ratio; VD/VT, dead space-to-tidal volume ratio; FEV_1, forced expiratory volume in 1 second.

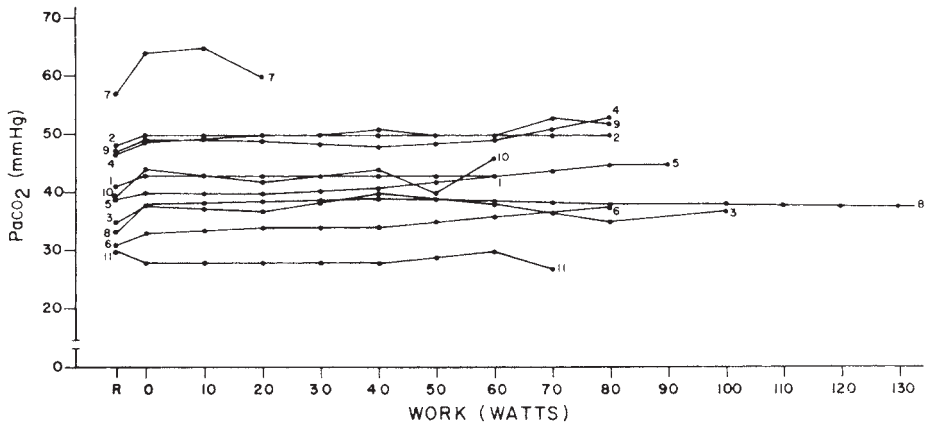

FIGURE 5.7. $Paco_2$ as related to work rate in 11 patients with stable chronic airflow obstruction (each point is a different work rate). The numbers on each curve identify the patient.

for a given $\dot{V}O_2$ (Table 5.10). Work output was reduced at a $\dot{V}O_2$ of 1 L/min in patients with COPD. Moreover, patients with COPD may develop a lactic acidosis at a relatively low work rate.[17,23] This is most likely due to the sedentary lifestyle of these patients. After training, the lactate level for a given work rate and the ventilatory requirement decreased for exercise.[17]

Dyspnea depends on a balance between how much air *must* be breathed to keep pace with metabolism and how much *can* be breathed. Patients with COPD, because of their increase in V_D/V_T, low work rate lactic acidosis, and hypoxemia, must breathe more to maintain blood gases and pH, but their peak ventilation is less than normal. Although many approaches have been taken to determine if patients with COPD are ventilatory limited, the breathing reserve has served this role very well. The maximal voluntary ventilation (MVV) measured at rest is easy to obtain and is a reasonable measure of the patient's ventilatory capacity. Work tasks requiring ventilation rates in excess of this value cannot be sustained. Thus, the breathing reserve, defined as the difference between the MVV and $\dot{V}_E$ at the maximum level of exercise that the subject could perform, is decreased to values close to zero in patients with COPD (Fig. 5.9). This contrasts with the large ventilatory reserve at the end of exercise found in most normal subjects[15,54,74] and, particularly, in patients with heart disease.

Examining the expiratory flow pattern can be useful in documenting airflow limitation. Typically, as shown in Figure 4.15, the pattern has an early expiratory peak and then a sustained expiratory flow until the point of inhalation, giving a trapezoidal appearance to the recorded pattern. No apneic pause occurs at the end of exhalation, in contrast to the finding in normal subjects when work

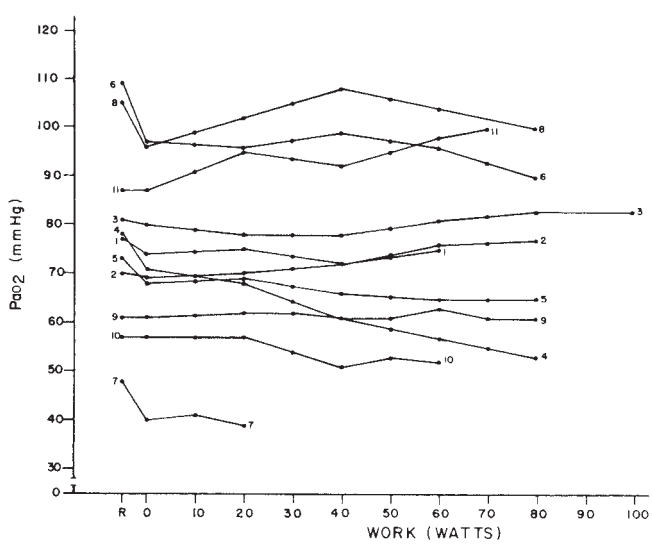

FIGURE 5.8. Pao_2 as related to increase in work rate for the same 11 patients shown in Figure 5.6 (each point is a different work rate). The numbers on each curve identify the patient and allow cross-correlation with each patient's $Paco_2$, shown in Figure 5.7.

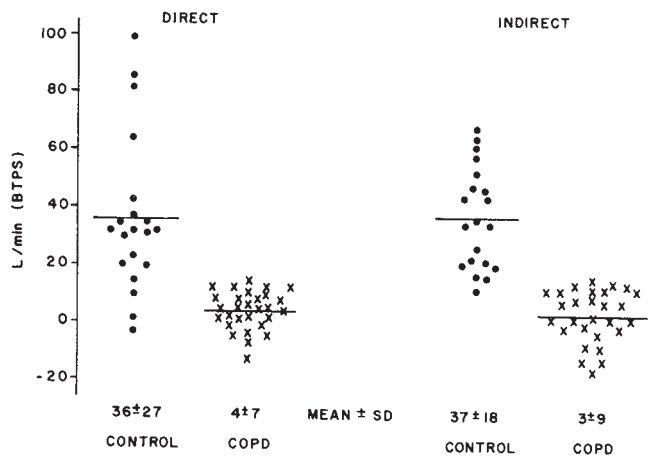

FIGURE 5.9. Breathing reserve (MVV–max $\dot{V}_E$) for a group of normal subjects and a group of patients with stable chronic obstructive pulmonary disease (COPD). The values under each column show the mean ± standard deviation. Measurements are made using the directly measured MVV and the indirectly measured MVV calculated by multiplying FEV_1 by 40. Note that the breathing reserve in patients with COPD is small and the standard deviation is narrow, reflecting the importance of airflow limitation in determining exercise intolerance.

rate is not excessively high. After effective bronchodilatation, the expiratory flow pattern normalizes, with the peak flow moving to the middle of the expiratory phase of respiration (see Fig. 4.15).

When patients develop air-trapping with exercise, the FRC increases, as evidenced by a reduction in the inspiratory capacity (Table 5.9). The inspiratory capacity can be measured during exercise by instructing the patient to take a maximum breath after a normal exhalation. This requires some practice to get reliable measurements in patients with obstructive lung disease and normal subjects. In contrast to the decrease in inspiratory capacity in patients with airflow obstruction, normal subjects have an increase in inspiratory capacity, suggesting that their FRC had decreased during exercise. Further evidence of air-trapping in COPD can be seen by a decrease in tidal volume as exercise work rate is increased (panel 7 in cases). Exercise-induced air-trapping increases, albeit not homogenously. The increase in alveolar pressure with airway closure in COPD increases the external work of the heart.

Whereas the peak $\dot{V}O_2$ is reduced in patients with uncomplicated obstructive lung disease, the $\dot{V}O_2$ usually does not decrease its rate of rise as work rate is increased in response to a progressively increasing work rate test in contrast to this frequent finding in patients with circulatory limitation. This is because ambulatory patients with stable obstructive lung disease are usually more limited in their ability to eliminate CO_2 (ventilatory limitation) than in their ability to make O_2 available to the mitochondria.

Often, patients with COPD develop a lactic acidosis at relatively low work rates because of their relatively untrained state (Table 5.10). Other patients with very severe airflow obstruction may not be able to exercise sufficiently to reach their *AT* and develop a lactic acidosis during exercise. Those patients who develop a significant lactic acidosis at a relatively low work rate should benefit most from skeletal muscle training because they have the potential to decrease the lactic acidosis stimulus to ventilatory drive.

The HR at maximum work rate is generally low (high HR reserve; Fig. 5.10), but maximum HR can be increased if the patient's maximum work rate can be improved through O_2 breathing or bronchodilatation. In contrast to cardiac disorders, O_2 pulse continues to increase normally with increasing work rate, although the final absolute values are usually reduced at peak exercise (Fig. 5.4).

Oxygen Transport–Oxygen Requirement Imbalance

To sustain exercise, ATP must be regenerated aerobically. Failure of the left ventricular output to meet the muscle O_2 demand for ATP regeneration at the rate required for the increasing work rate will force the patient to stop exercise due to muscular fatigue. An inadequate transport of

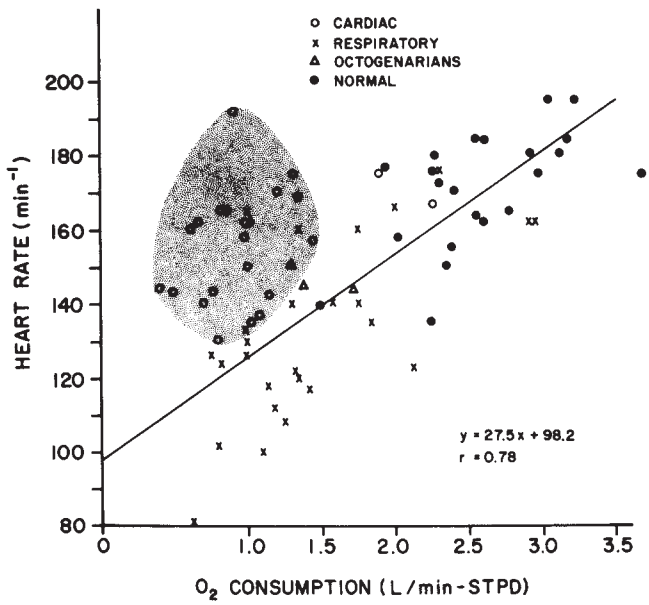

FIGURE 5.10. Heart rate at maximal exercise for normal subjects, octogenarians, and patients with chronic respiratory disease or cardiac disease. The normal subjects reach a higher maximum heart rate and $\dot{V}o_2$. Note that the octogenarians fall on the same slope as the younger normal subjects, although their maximum heart rate and maximum oxygen uptake are less. Similarly, the patients with respiratory defects have a still lower maximum oxygen uptake and heart rate. The cardiac patients (*stippled area*) have a higher maximum heart rate relative to the maximum O_2 uptake than that of the other subjects. (From Wasserman K, Whipp BJ. Exercise physiology in health and disease [state of the art]. *Am Rev Respir Dis.* 1975;112:219–249, with permission.)

O_2 to muscles relative to its requirement will be reflected in a decreased peak $\dot{V}O_2$ and a reduced rate of increase in $\dot{V}O_2$ as work rate increases. The following mechanisms underlie the failure of left ventricular output to keep pace with the increased O_2 requirement of a progressively increasing work-rate test in patients with COPD:

1. *Positive intrathoracic pressure.* Large positive pressures develop in the chest during exhalation in patients with poor lung elastic recoil and hyperinflation (patients with emphysema). Thus, intrathoracic pressure increases during exhalation, limiting diastolic (atrial) filling and stroke volume. As breathing frequency increases during exercise in COPD, expiratory muscles contract to accelerate exhalation of respired gases. This process becomes more marked as breathing rate increases to maintain arterial blood gas homeostasis. This impediment to venous return to the heart can account for the relatively low cardiac output and stroke volume observed in emphysema patients during exercise.
2. *Increased pulmonary vascular resistance.* Increased pulmonary vascular resistance might also cause left ventricular output to be inadequate to meet the increased O_2

needed for aerobic regeneration of ATP during exercise. Many patients with emphysema have significantly elevated pulmonary vascular resistance that, although not limiting at rest, might prevent the right ventricle from increasing blood flow through the pulmonary circulation at the rate needed to meet the muscle O_2 requirement during exercise.

3. *Coexistent factors, such as primary heart disease and reduced arterial oxygen content.* Patients with lung diseases might also have primary heart disease that limits the ability of the circulation to increase O_2 transport at the rate needed to perform exercise. Other mechanisms that contribute to the impairment of O_2 flow to the muscles, such as reduced arterial O_2 content due to reduced Pa_{O_2}, anemia, and carboxyhemoglobinemia, when combined with the pathophysiology of COPD, might worsen symptoms of fatigue and/or dyspnea beyond that expected from the degree of the underlying pathophysiology.

Physiological Markers of Inadequate Oxygen Transport

Although respiratory mechanics are significantly impaired in patients with COPD, it is imperative to evaluate exercise gas exchange in these patients in order to determine if reduced O_2 transport is caused by impaired ventilatory mechanics or by metabolic changes with increased ventilatory drive characteristic of heart failure. The increased ventilatory drive in these patients results from the increased H^+ accompanying the increased lactate, as well as the CO_2 released by the increased rate of buffering lactic acid. Thus, in the presence of reduced O_2 transport, the *AT*, $\Delta\dot{V}O_2/\Delta WR$, as well as the peak $\dot{V}O_2$ are likely to be reduced.

Restrictive Lung Diseases

Patients with restrictive lung disease due to pulmonary fibrosis generally are exercise limited because of dyspnea or fatigue or both (Table 5.11). Study of the pathophysiology of these patients reveals that they have disturbed lung mechanics and a reduction in the functional pulmonary capillary bed (Fig. 5.11). Hansen and Wasserman,[32] in a study of a population of patients with interstitial lung diseases of mixed etiology, found that most of the patients were limited by their inability to increase pulmonary blood flow appropriately in response to exercise (Fig. 5.11, right pathway leading to exercise limitation). Not only did their patients have a reduced peak $\dot{V}O_2$, but the *AT* was also usually reduced. In contrast to patients with COPD, $\Delta\dot{V}O_2/\Delta WR$ was reduced, with the slope of the relationship becoming shallower as peak $\dot{V}O_2$ was approached.

Pulmonary fibrosis of the idiopathic type (IPF) develops from chronic lung inflammation.[25] The pathologic features are usually nonuniform, so some acini, including their blood supply, are completely replaced by scar tissue. In contrast, neighboring units that are less involved or uninvolved may undergo compensatory hyperinflation. From the point of view of lung mechanics, the net effect of the pathophysiology of IPF is a reduction in the total number of functioning acini and, consequently, a relatively poorly compliant small lung.[36] However, both the total lung capacity and its subcompartments are reduced, predominantly that of the inspiratory capacity. Thus, the extent to which the tidal volume can increase with exercise is limited, and the patient must increase breathing frequency to a value higher than normal to meet the ventilatory requirement for exercise. Consequently, the V_T/IC ratio is high and approaches 1. The breathing frequency at maximum exercise often exceeds 50 breaths per minute. Such high breathing frequencies are unusual in patients with COPD because it will cause more air-trapping and hyperinflation. Ventilation at the maximum work rate may approach the MVV if the patient is not limited by the inability to increase cardiac output earlier because of the restricted pulmonary capillary bed. However, often the pathophysiology reflects both a failure to increase $\dot{V}O_2$ appropriately for the work rate performed and an increased ventilatory response due to exercise lactic acidosis, hypoxemia, and ventilation–perfusion mismatching (increased V_D/V_T).

Early in the pathophysiologic development of interstitial lung diseases, it appears as though the pulmonary capillary bed is functionally reduced and normal recruitment of more capillary bed in response to exercise fails to occur. This restricted capillary bed results in a shortened red cell transit time in the pulmonary capillaries as the exercise work rate is increased. The progressive reduction

Table 5.11

Discriminating Measurements during Exercise in Patients with Restrictive Lung Diseases

Low peak $\dot{V}O_2$
High V_T/IC
Breathing frequency >40 at max WR
Low breathing reserve
High V_D/V_T
High $P(a-ET)CO_2$
High $\dot{V}E/\dot{V}CO_2$ at *AT*
Pa_{O_2} decreases and $P(A-a)O_2$ increases as WR is increased
$\Delta\dot{V}O_2/\Delta WR$ is reduced

IC, inspiratory capacity; WR, work rate; $P(a-ET)CO_2$, arterial-end tidal P_{CO_2} difference; $\dot{V}E/\dot{V}CO_2$ at *AT*, ventilatory equivalent for CO_2 at anaerobic threshold; $P(A-a)O_2$, alveolar–arterial P_{O_2} difference; $\Delta\dot{V}O_2/\Delta WR$, increase in $\Delta\dot{V}O_2$ relative to increase in work rate.

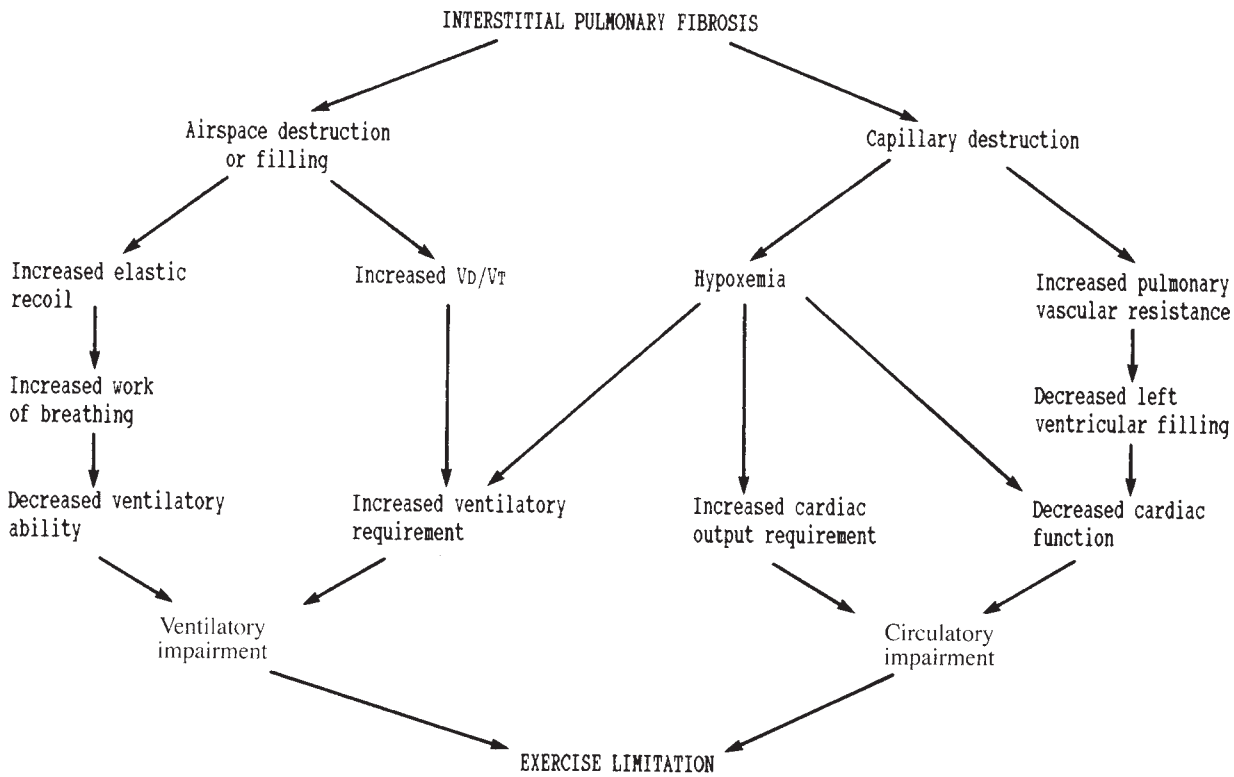

FIGURE 5.11. Pathophysiology of exercise limitation in patients with interstitial lung disease and idiopathic pulmonary fibrosis. (From Hansen JE, Wasserman K. Pathophysiology of activity limitation in patients with interstitial lung disease. *Chest.* 1996;109:1566–1576, with permission.)

of the red cell residence time in the pulmonary capillary as work rate and cardiac output increase results in a systematic decrease in Pa_{O_2} as $\dot{V}_{O_2}$ increases, similar to that seen in pulmonary vascular occlusive disease. This systematic decrease in Pa_{O_2} is usually not seen if pulmonary blood flow ($\dot{V}_{O_2}$) fails to increase and in COPD (Fig. 5.8). Low $\dot{V}_A/\dot{Q}$ regions of the lung might also contribute to the hypoxemia in patients with pulmonary fibrosis.[25] The ventilatory response of patients with pulmonary fibrosis is steep, partly because of a reduced Pa_{CO_2} set point in some subjects, but mainly because of an increased V_D/V_T in all subjects. Worsening hypoxemia as work rate is increased, elevated dead space ventilation caused by uneven ventilation–perfusion ratios, increased lactic acidosis from impaired O_2 transport, and a reduced ability to increase tidal volume leading to rapid shallow breathing contribute to dyspnea in the IPF patient (Fig. 5.11). In addition, exercise fatigue might be brought about by the inability to provide O_2 to the skeletal muscles at a rate sufficient for the exercise work rate to be performed aerobically.

Pulmonary alveolar proteinosis is a good example of exercise hypoxemia that is primarily due to a diffusion defect.[72] This disease results in alveolar filling by a semisolid proteinaceous material. Pulmonary fibrosis is minimal or nonexistent. Frequently, the vital capacity and total lung capacity are only slightly reduced and FEV_1/FVC is normal. Because the mean path length from lung gas to lung capillaries is increased in this disorder by a medium unfavorable for O_2 diffusion, this barrier limits the mass flow of O_2 into the pulmonary capillaries. During exercise, when red cell transit time in the capillary bed is reduced and its residence time shortened, less time is available for diffusion equilibrium. Thus, the major findings in this disorder are a systematic decrease in Pa_{O_2} and an increase in $P(A-a)_{O_2}$ with increasing work rate.[76]

Chest Wall (Respiratory Pump) Disorders

Disorders of the respiratory pump include muscle weakness, chest deformities, rigidity of the thoracic cage (as in ankylosing spondylitis), muscle and motor nerve disorders, and extreme obesity. Patients with these disorders, like those with restrictive pulmonary disorders, have a limited ability to increase V_T (Table 5.12). Although their lungs are essentially normal, the maximal intrapleural pressure available to expand the lungs is insufficient to allow V_T to increase normally as work rate is increased. Therefore, to obtain the increase in $\dot{V}_E$ required for exercise, these patients must increase breathing frequency predominantly.

Table 5.12

Discriminating Measurements during Exercise in Patients with Chest Wall Disorders

Low peak $\dot{V}O_2$
High VT/IC
High breathing frequency
Low breathing reserve
High heart rate reserve

VT, tidal volume; IC, inspiratory capacity.

The reduced maximum $\dot{V}O_2$ defines the degree of exercise limitation. The $\dot{V}O_2$ increases normally with increasing work rate. Because the lung parenchyma is essentially normal, PaO_2 is usually normal and does not decrease as the work rate is increased. The breathing reserve is low when symptom-limited exercise is reached (usually due to dyspnea). Because of impaired ventilatory mechanics, these patients usually do not develop normal ventilatory compensation for the lactic acidosis of exercise. HR reserve is high at maximal exercise because the cardiovascular system cannot function fully due to the breathing limitation.

DEFECTS IN HEMOGLOBIN CONTENT AND QUALITY

As described in Chapter 1, a considerable increase in O_2 flow from the atmosphere to the mitochondria is essential for the normal exercise response. This function is critically dependent on the ability of the circulation to transport O_2 from the lungs to the exercising muscles. Therefore, it is appropriate to consider how changes in the properties of blood might impair O_2 delivery to the mitochondria and thereby reduce exercise capacity (Table 5.13).

Because cardiac output and HR during exercise are determined by the O_2 requirement, patients with a reduced blood O_2 carrying capacity commonly have a relatively high cardiac output and HR for a given work rate (i.e., a relative tachycardia). The stroke volume is normal or even increased, in contrast to patients with cardiac diseases and disorders of the pulmonary circulation. Because the arterial O_2 content is low, the ability to increase arterial–venous O_2 difference in response to exercise is reduced. Consequently, the maximum O_2 pulse (product of stroke volume and $C[a - \bar{v}]O_2$) is reduced. As in other disorders of reduced maximal O_2 flow, the maximum $\dot{V}O_2$ and *AT* are also reduced. Table 9.2 describes the reduction in maximal $C(a - \bar{v})O_2$ as related to reduced hemoglobin concentration. From this and peak $\dot{V}O_2$, the cardiac output and stroke volume

Table 5.13

Discriminating Measurements during Exercise in Patients with Anemia, Increased Carboxyhemoglobin, or Hemoglobinopathies

Low peak $\dot{V}O_2$
Low *AT*
Low O_2 pulse
Normal VD/VT, $P(a - ET)CO_2$, and $P(A - a)O_2$
Tachycardia and steep heart rate versus $\dot{V}O_2$ relationship

AT, anaerobic threshold; VD/VT, physiological dead space/tidal volume ratio; $P(a - ET)CO_2$, arterial–end tidal PCO_2 difference; $P(A - a)O_2$, alveolar–arterial PO_2 difference.

can be estimated at peak exercise. Specific mechanisms of reduced arterial O_2 content are described in the following sections.

Anemia

Because anemia results in a reduced blood O_2 carrying capacity, it compromises O_2 delivery to the mitochondria (Fig. 5.1). With anemia, the exercising muscle capillary PO_2 falls more rapidly than normal during the transit of blood from artery to vein (see Fig. 2.15). Thus, the diffusion gradient of O_2 from the blood to the mitochondria decreases more rapidly than in nonanemic conditions. Consequently, a critically low capillary PO_2 may be reached at a lower $\dot{V}O_2$ than normal, necessitating anaerobic mechanisms for ATP regeneration, with increasing lactate concentrations and metabolic acidosis (see Fig. 2.1).

Subjects with anemia commonly experience breathlessness during exercise. Although the arterial O_2 content is low, the arterial PO_2 is not reduced. Because the carotid bodies respond to arterial PO_2 and not O_2 content, the reduced O_2 content is not itself the cause of the increased ventilatory drive and, therefore, cannot account for the symptom of breathlessness. More likely, the breathlessness and increased ventilatory drive with exercise in the anemic patient are due to the metabolic acidosis that accompanies the patient's low *AT*. The acidemia results in an increased ventilatory drive (mediated by the carotid bodies) and a relatively high minute ventilation at a low maximum work rate.

The role of anemia in the reduction of $\dot{V}O_2$ can be calculated when the subject is normoxic. Indeed, because each gram of hemoglobin binds 1.34 mL of O_2 and because, at peak exercise, O_2 extraction is ~75%, each gram of hemoglobin delivers 1 mL of O_2. Thus, for example, if cardiac output is 10 L per min, each 1 g hemoglobin per dL accounts for 100 mL per min of $\dot{V}O_2$.

Left-Shifted Oxyhemoglobin Dissociation Curve

Conditions that cause a leftward shift in the oxyhemoglobin dissociation curve (reduced P_{50}), such as some hemoglobinopathies, a decrease in 2,3-DPG due to a defect in red cell metabolism, an increase in carboxyhemoglobin, or increased glycosylated hemoglobin found in poorly controlled diabetic patients, should cause the capillary blood P_{O_2} to decrease more rapidly than normal.[11] Thus, the P_{O_2} difference between capillary and mitochondrion may reach a critical value at a reduced work rate. Consequently, O_2 flow through the exercising muscle may not provide the O_2 needed by the mitochondria to support ATP regeneration at the subject's predicted *AT*. Thus, anaerobic regeneration of ATP would be needed to support the energy requirement at a relatively low work rate. Exercise studies on patients with a left-shifted hemoglobinopathy support the concept that these disorders lead to anaerobic glycolysis and increased net lactate production at reduced work rates.[14]

Carboxyhemoglobinemia and Cigarette Smoking

Carboxyhemoglobinemia from exposure to carbon monoxide results in a reduced O_2-carrying capacity. When the carboxyhemoglobin level is increased, arterial oxygen content is reduced. In addition, carbon monoxide causes a leftward shift in the oxyhemoglobin dissociation curve. This reduces the peak $\dot{V}O_2$ and *AT*.[33,43,55,71]

Cigarette smoking adversely affects exercise tolerance by its effects on the blood, the cardiovascular system, and the lungs. HR, blood pressure, and the double product (HR times systolic blood pressure) are increased when one performs exercise immediately after smoking.[33] Ventilation–perfusion relations become abnormal, as evident from the increased $P(a-ET)CO_2$ during exercise. While short-term cigarette smoking did not have an immediate effect on airway resistance in young men, it was observed to cause acute cardiovascular changes and changes consistent with worsened $\dot{V}A/\dot{Q}$ mismatch.[33]

CHRONIC METABOLIC ACIDOSIS

Chronic metabolic acidosis, with a reduced blood $[HCO_3^-]$, can result from poorly controlled diabetes, chronic renal failure, or primary renal tubular acidosis, or secondary to treatment of glaucoma with a carbonic anhydrase inhibitor (acetazolamide) (Table 5.14). To restore normal arterial pH due to the decrease in arterial $[HCO_3^-]$, ventilation is stimulated, presumably by H^+, until arterial P_{CO_2} is reduced to a new lower P_{CO_2} set point, bringing pH close to 7.4.[35,51] The magnitude of the increase in ventilation is approximately proportional to the reduction in $[HCO_3^-]$ and Pa_{CO_2}. To maintain the reduced Pa_{CO_2} during exercise, the $\dot{V}CO_2$ and ventilation must increase hyperbolically. The higher the work rate, the higher the additional ventilation. The increased ventilatory requirement needed to maintain the arterial pH, when arterial $[HCO_3^-]$ is reduced, leads to an apparent increase in "sensitivity" of the respiratory control mechanism.

Table 5.14

Discriminating Measurements during Exercise in Patients with a Chronic Metabolic Acidosis

Low $[HCO_3^-]$
Steep $\Delta\dot{V}E/\Delta\dot{V}CO_2$ relationship
Normal $P(A-a)O_2$ and $P(a-ET)CO_2$
Normal VD/VT
Low breathing reserve

$P(A-a)O_2$, alveolar–arterial P_{O_2} difference; $P(a-ET)CO_2$, arterial–end tidal P_{CO_2} difference; VD/VT, physiological dead space/tidal volume ratio.

The presence of a chronic metabolic acidosis before exercise begins is evident from the resting arterial blood gases. The $[HCO_3^-]$ and Pa_{CO_2} are reduced, and pH is only slightly reduced or normal. During exercise, $\dot{V}E$ increases proportionally with the increase in CO_2 production (Fig. 2.43). Because the slope of the $\dot{V}E$–$\dot{V}CO_2$ relationship is steeper, the lower the Pa_{CO_2}, the effect of the metabolic acidosis is to amplify the ventilatory response as work rate is increased (see Figs. 2.44 and 4.17). Without measuring arterial blood gases, a relatively steep slope relationship between $\dot{V}E$ and $\dot{V}CO$ during exercise, with R in the normal range, signifies either chronic hyperventilation or increased VD/VT. Arterial blood gas and pH measurements differentiate these two potential causes of a high ventilatory response.

By itself, chronic metabolic acidosis is not a prominent cause of dyspnea. However, in conjunction with other disorders, such as obstructive airways disease, it may lower the CO_2 set point to such a marked degree that the ventilatory requirement to perform a given work rate may exceed the subject's MVV. In this case, the sensation of dyspnea would be high. Correction of the metabolic acidosis might reduce the ventilatory requirement below the subject's MVV and relieve the sensation of dyspnea.

MUSCLE DISORDERS AND ENDOCRINE ABNORMALITIES

Little information is available concerning the metabolic cost of exercise in patients with primary muscle disorders. Because of reduced motor efficiency, patients with neuromuscular disorders with accompanying spasticities

and motor incoordination presumably have an increased O_2 requirement for performing physical work. We have not had the opportunity to evaluate these patients in the exercise laboratory.

Certain muscle enzyme deficiencies limit exercise performance. For example, patients with inability to use muscle glycogen because of myophosphorylase deficiency (McArdle syndrome)[48] or other disease of the glycolytic pathway[47] are unable to exercise to work levels that normally require anaerobic mechanisms to supplement the energy generated by aerobic mechanisms. These patients experience severe muscle pain and the release of myoglobin and creatine kinase from muscle when attempting to exercise at levels that normally induce a lactic acidosis. The $\dot{V}O_2$–work rate relationship appears to be normal for work rates below the level that induces pain in these patients.[57] The maximum work capacity of these patients is limited to work rates near the *AT* of normal sedentary subjects. Thus, their peak $\dot{V}O_2$ is on the order of 1 L per min. Their ventilatory response to exercise is generally normal,[57] although it has also been reported to be high.[28] The HR and cardiac output responses of these patients are inordinately high for the metabolic rate, and the arterial–venous O_2 difference at maximal work rate is low[46] because of the failure to extract O_2, normally secondary to the absence of the normal exercise lactic acidosis. The latter does not allow the full rightward shift in the oxyhemoglobin dissociation curve and normal O_2 unloading from hemoglobin (Bohr effect) in the capillary bed. The Bohr effect is needed for the normal maximal O_2 extraction from blood during exercise.[75]

Patients with mitochondrial electron transport chain defects develop lactic acidosis at exceptionally low work rates.[10,29] In contrast with myophosphorylase-deficient patients, however, the gas exchange abnormalities accompanying these metabolic defects have not been well studied. Nevertheless, it is recognized that the gas exchange abnormalities likely differ from those seen with defects in the glycolytic pathway and resemble those found in patients with heart failure. Thus, lactate and CO_2 output from bicarbonate buffering increase relative to O_2 uptake at reduced work rates.[10]

Diabetes mellitus affects large arteries (atherosclerosis), small blood vessels, and capillaries. When the disease is poorly controlled, patients with diabetes also have a leftward shift in the oxyhemoglobin dissociation curve (glycosylated hemoglobin). Any and all of these abnormalities could cause a reduction in *AT* and peak $\dot{V}O_2$.[45] Studies in children with diabetes suggest that the *AT* and peak $\dot{V}O_2$ are reduced even when the patient's diabetes is under good control.[9,59,64]

Patients with poorly regulated diabetes increase their use of fatty acids for energy. During exercise, use of fatty acids by muscle, in contrast to the normally preferred carbohydrate, should make the patients with poorly controlled diabetes require slightly more O_2 for the same energy production. Figure 2.3 illustrates the effect of the proportion of carbohydrate to fatty acid in the metabolic substrate mix on metabolic efficiency with respect to O_2 consumption to energy yield during exercise.

The ventilatory response to exercise has been demonstrated to be increased and the $PaCO_2$ reduced in women during the progestational phase of the menstrual cycle. The effect of this increased ventilatory drive on maximal exercise performance in women is unknown.

PSYCHOGENIC CAUSES OF EXERCISE LIMITATION AND DYSPNEA

Anxiety Reactions

Anxiety reactions occasionally cause dyspnea during exercise. One manifestation of anxiety is intense hyperventilation with development of acute respiratory alkalosis. The hyperventilation pattern is unique in that the breathing frequency is high and quite regular. In addition, the tachypnea starts abruptly, as though switched on, rather than gradually, as is normally seen during progressive exercise. Hyperventilation might actually start at rest, in anticipation of the exercise. Psychogenic dyspnea might also be evident as rapid and unusually shallow breathing. Usually P_{ETCO_2} is very low and P_{ETO_2} is high in the early phase of exercise. If the subject is unable to maintain the high exercise ventilation, exceptionally low P_{ETCO_2} and high P_{ETO_2} these values may gradually change in the normal direction toward the end of exercise. In such a case, the R ($\dot{V}CO_2/\dot{V}O_2$) increases at the beginning of exercise and decreases toward the patient's symptom limited maximum work rate.

Another manifestation of an anxiety reaction described as shortness of breath may, in fact, be irregular breathing or breath holding. Observing the behavior pattern and the patient's facial expression may be helpful in detecting this problem.

Poor Effort and Manipulated Exercise Performance

It is important to distinguish manipulated exercise performance from other disorders. An exercise test in which both HR reserve (see panel 2, Fig. 4.32) and breathing reserve (see panel 7, Fig. 4.32) are high and the *AT* is not reached (see panel 5, Fig. 4.32) strongly suggests poor effort. However, inadequate effort may also be evident when the *AT* is normal, accompanied by a high HR reserve and breathing reserve without the normal increase in R expected during a progressively increasing work rate test (panel 8, Fig. 4.32).

A chaotic breathing pattern (panel 7, Fig. 4.32) supports manipulation of the exercise test. Normally, ventilation,

tidal volume, and breathing frequency increase in a distinct systematic pattern, increasing tidal volume primarily with increasing $\dot{V}E$, below the *AT*, and then increasing breathing frequency above the *AT*. A chaotic breathing pattern and psychogenic dyspnea are most readily diagnosed during exercise when gas exchange is monitored breath by breath.

Before stating that a claimant for disability is not impaired on a pulmonary basis, it is often necessary to sample arterial blood sequentially for measurement of lactate increase, as well as to confirm a normal $P(A-a)O_2$, $P(a-ET)CO_2$, and VD/VT during exercise. Also, arterial blood gas and pH measurements are needed during exercise to document whether the arterial blood gas changes are consistent with that of a normal person, a person with obesity, a person with lung disease, or a person who is manipulating ventilation.[3] Variable and inconsistent changes in breath-by-breath measurements of $PETCO_2$ and $PETO_2$ provide evidence for manipulated exercise performance (see panel 9, Fig. 4.32).

COMBINATIONS OF DEFECTS

A patient's symptoms may be more marked than predicted from the nonexercise assessment of the severity of the patient's disease. This might be noted particularly when the primary disease is combined with a complicating problem, such as cigarette smoking or use of a drug that affects ventilatory drive directly or indirectly through a metabolite (e.g., H^+). Thus, patients with coronary artery disease who have hypertension, are sedentary, and smoke might be less symptomatic and have better exercise tolerance if their blood pressure were under adequate control, were physically active, and did not smoke. Thus, the combined defects may cause the patient to be more symptomatic than if the two diseases did not coexist. When more than one disease is present that can cause the same symptom(s) during exercise, a cardiopulmonary exercise test is probably the best way to identify, which disease is the primary contributor to the patient's symptoms, as well as to provide a noninvasive, relatively inexpensive method to assess the efficacy of therapy.

SUMMARY

The major function of the cardiovascular and ventilatory systems is gas exchange between the cells and the atmosphere. Therefore, impairments in cardiovascular and respiratory function are most apparent during exercise because cell respiration is stimulated and defects are amplified. Because each component of the gas transport system that couples external to internal respiration has a different role, the pattern of the gas exchange abnormality differs according to the pathophysiology. Recognition of these differences allows the examiner to distinguish which organ system most likely accounts for the patient's exercise limitation. Thus, whereas primary heart disease and primary lung disease both cause a reduction in work capacity, the patterns of the gas exchange responses differ. By making measurements that address the gas transport function at each site in the coupling of external to cellular respiration, it is possible to deduce the physiological state of each component.

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CHAPTER

6

Clinical Exercise Testing

EXERCISE LABORATORY AND EQUIPMENT

General Laboratory Environment

The proper interpretation of exercise test data depends on accurate data collection and correct calculations. Useful exercise testing can be performed with little or no equipment. A measured course, stairway, or hallway can provide a reproducible and functional exercise stress. After review of symptoms and physical examination, information collected might include heart and ventilatory rate and blood pressure at the conclusion of exercise. However, a properly equipped laboratory, with gas exchange measurement, blood pressure, and electrocardiographic capability, provides more complete data collection. The patient can be relatively stationary on an ergometer during a controlled and reproducible stress while measurements are continuously monitored, and blood may be sampled. Figure 6.1 diagrams the devices and measurements that are generally available in a modern exercise laboratory.

The laboratory should be air-conditioned and regulated at a comfortable temperature and humidity. The patient's view should be pleasant and not cluttered with tubing, wires, or a bulletin board with distracting papers. If blood is to be sampled, the syringes should be prepared and placed in a convenient location to avoid confusion or extra motion during the time of the study. The number of people in the laboratory should be limited to those needed for making the measurements and for patient safety. Finally, extra sounds should be kept to a minimum. Soft background music helps to dampen noise but does not interfere with communication between the examiner and the technician. In summary, a pleasant, professional environment is needed to obtain the maximum confidence and therefore performance by the patient.

Gas Exchange Measurement

Although exercise testing can be performed with little or no equipment, the more sophisticated and potentially useful analysis of cardiopulmonary function during exercise necessitates gas exchange measurement. A variety of systems, measuring devices, recorders, and other equipment have been put together for these purposes. There are excellent commercial systems that determine gas exchange using either a gas-mixing chamber or, more commonly, breath-by-breath analysis of respired gas.

Mixing Chambers

In systems using a mixing chamber, expired ventilation is determined using a flow or volume measurement device, while expired gas is passed into a fixed or variable-sized mixing chamber from which gas is sampled and analyzed for O_2 and CO_2 concentrations. With proper mixing of

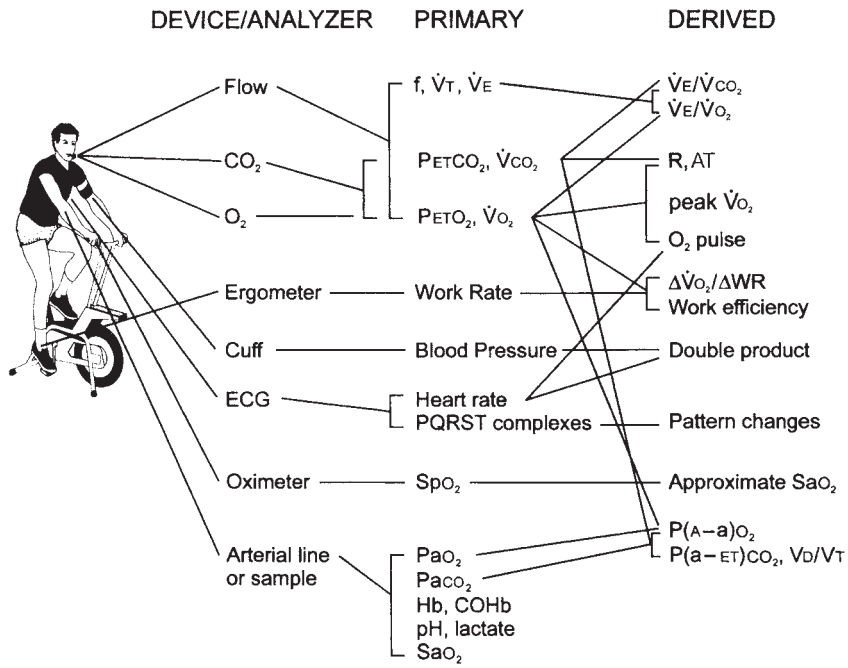

FIGURE 6.1. Devices and analyzers used to measure variables during exercise on a cycle ergometer. Devices and analyzers individually or collectively may measure a single or several primary variables. The variables in the right-hand column are usually calculated from two or more primary variables.

expired gas from each breath, differences in O_2 and CO_2 concentration from the beginning to the end of each breath are minimized, and the resultant O_2 and CO_2 concentrations are equal to the volume-weighted average or "mixed expired" concentrations. These are equivalent to the O_2 and CO_2 concentrations that would have been obtained by collecting all of the expired gas in a bag.

A theoretically ideal mixing chamber would be of sufficient size for complete mixing of each whole breath. It would provide a gas composition identical to that of the mixed expired gas for the series of whole breaths corresponding to the time of expired flow measurement. A large gas flow (or minute ventilation) or a mixing chamber of small size has a short time constant. Under these conditions, this chamber would respond rapidly to a change in gas concentration; however, the small volume means that a subject with a large tidal volume will produce marked fluctuations in gas concentrations in the chamber. Thus, the size of the mixing chamber relative to the size of the tidal volume is critical. Too large a mixing chamber volume compared with tidal volume results in an impracticably long time to reach any new equilibrium, making the mixing chamber poorly responsive to changes in gas concentration. A fixed-volume mixing chamber may be satisfactory during exercise when $\dot{V}E$, $FECO_2$, and FEO_2 change slowly, but may not be satisfactory when rapid changes are expected. If ventilation is continuously measured, a time or volume adjustment must be made to match the correct mixed expired gas concentrations with the correct ventilation.

Breath-by-Breath System

A breath-by-breath system measures airflow or volume continuously, and simultaneously determines instantaneous expired CO_2 and O_2 concentrations. After time alignment of O_2 and CO_2 concentrations with the instantaneous flow, the CO_2 output and O_2 uptake for each breath are calculated, as described by Beaver et al.[12] $\dot{V}CO_2$ and $\dot{V}O_2$ are calculated for the respective breath by cross-multiplying volume (integrated flow), every 0.01 to 0.03 seconds, by the time-corrected gas concentration. If required for a cumulated average for 10 seconds, the second-by-second interpolation of the breath-by-breath data is averaged for the 10 one-second samples over the relevant time period. To make accurate measurements, ventilation and gas concentrations must be determined as near to continuously as possible. We have used breath-by-breath systems for both research applications and for evaluation of patients.[12,77,83] Commercially available systems make it possible to determine gas exchange rapidly and accurately under many conditions. By interpolating breath-by-breath expired volume, O_2 uptake, and CO_2 output, second by second, it is possible to reduce the variability in breath-by-breath measurements. If necessary, replicate studies with time-averaging of the second-by-second values can be performed[12,77,83] to enhance the measurement of physiological responses to rapid changes in work rate.

Measurement of Volume, Flow Rate, or Ventilation

Several methods of measuring respired gas volume and flow rates during exercise are used. Although expired flow is usually measured with a flowmeter and integrated into volume, physiological variables can also be calculated from inspired volume or flow with the appropriate mathematical adjustment to convert to expired volume. Devices for measuring volume or flows may be used directly as

part of the breathing circuit. If the device is used directly, then flow resistance, linearity, and frequency response may be important considerations.[35] Commercially used flow devices include pneumotachographs, Pitot tubes, turbines, and hot-wire anemometers. Volume can be measured directly using a gas meter, spirometer, or volume transducer.

Pneumotachographs consist of a number of parallel tubes to linearize flow (Fleisch type) that offer a small resistance to gas flow. Gas flow is directly proportional to pressure drop across the resistance when flow is laminar, and the relationship is given by Poiseuille law. When flow becomes nonlaminar or turbulent, the relationship between flow and pressure becomes nonlinear. In a Fleisch pneumotachograph, laminar flow is encouraged by small flow channels and low gas velocities. Small flexible plastic tubes are connected at each end of the resistance element, and these two tubes are connected to a differential pressure transducer. The Fleisch-type pneumotachographs come in different sizes to accommodate for the flow rates expected.

For exercise testing in adult patients, flows encountered generally indicate that a size no. 3 Fleisch pneumotachograph is appropriate.[35] Compensation for documented nonlinearities in the pressure–flow relationship can be made by altering the output of the differential pressure transducer either electrically or mathematically using a computer. In commercial systems, empirical calibration curves may be used to optimize pneumotachograph performance.

Because expired gas is usually warmer and contains more water vapor than ambient air, contact of warm expired gas with an ambient-temperature pneumotachograph could result in condensation and obstruction of the pneumotachograph resistance elements. Pneumotachographs, therefore, are often used with an electric heater to warm the pneumotachograph to a temperature slightly above expired gas. However, a heated pneumotachograph not only warms and increases the volume of the expired gas, but also warms it by a variable amount depending on the flow. Although theoretic methods can be used to estimate the degree of warming, two practical methods may eliminate the problem. In the first method, the expired gas is kept warm, and the temperature of the pneumotachograph is only slightly warmer (0.5° C) than the temperature of the gas passing through it. Another way is to distance the pneumotachograph from the mouth so that it can be allowed to cool to ambient temperature before flow is measured.

Pitot tubes[64] measure the difference in pressure at an opening placed directly facing the flow stream compared with the pressure at an opening perpendicular to the flow stream (static pressure). From Bernoulli law, the velocity of flow movement is proportional to the square root of the pressure difference; from the cross-sectional area of the device, the flow can be calculated. The Pitot tube has the advantage of being nonresistive and dependent on turbulent flow rather than on laminar flow conditions. A flowmeter suitable for exercise gas exchange measurements based on the Pitot tube principle uses a differential pressure transducer to determine the pressure difference between the static and midstream ports. A suitable algorithm calculates the flow from the pressure signal and also corrects for nonlinearities over the flow measurement range. Advantages of such a device include low resistance, lack of a requirement for laminar flow, and minimal problems with heating or cooling of inspired or expired gas.

Turbine flowmeters and hot-wire anemometers[94,95] can also be used to measure the mass or flow of gas. The latter device determines the change in amount of electrical current, compared with baseline, needed to maintain a constant temperature of a wire placed in the air stream. The wire material is selected so the wire resistance is strongly influenced by the wire temperature. The rate of mass movement of gas and its thermal capacity relate to the current change; by using an appropriate model, the flow of gas can be calculated. Although this method is inherently nonlinear, digital computer algorithms can correct this nonlinearity.

Breathing Valves, Mouthpieces, and Masks

Some gas exchange measurement systems require the use of a breathing valve to separate inspired from expired gas flows so expired gas can be collected and analyzed. The ideal valve prevents contamination of either inspired or expired gas flow by the other, has no resistance to breathing, has low rebreathed volume (low valve dead space), is of minimal weight and size, is easily cleaned and sterilized, is low cost, does not generate turbulence, and operates silently.

Dead space for the valve plus attached mouthpiece can be determined by measuring the volume of water it can hold. Valve resistance can be determined during constant airflow using a pressure transducer and flowmeter. Valves may develop backleaks, especially when subjected to high flows and pressures during heavy exercise. These leaks should be suspected for any valve, but especially after prolonged use, excessive secretions, or damage to component parts. Errors in ventilation or gas exchange measurements may be important clues to a leaking breathing valve. If a leak is suspected, simultaneous recording of inspiratory and expiratory flow during exercise may reveal the presence and location of the leak.

Traditionally, patients have used nose clips so that all inspired and expired gases are routed through rubber or soft plastic mouthpieces. Now, comfortable face masks of differing sizes and shapes to cover the patient's nose and mouth are available. The dead space is usually only slightly more than with a mouthpiece and nose clip.

Gas Analyzers

For gas exchange measurements, the concentration of O_2 and CO_2 in the expired gas can be determined by several devices. Mass spectrometers convert sampled gases to positively charged ions with an electron beam. Then, in a near vacuum, the ions are accelerated by an electric field and are then subjected to a magnetic field. The direction that the ions take in the magnetic field is dependent on their mass-to-charge ratios. The different ions representing different gases are detected by appropriately located detectors that each produce a voltage output proportional to the number of ions that strike the collector per unit time. Because the total voltage is dependent on the sum of the individual detector voltages, any gas for which there is no detector does not contribute to the total. For respiratory mass spectrometry, detectors for O_2, CO_2, and N_2 are typically used; however, there are no detectors for water vapor, argon, or other inert gases present in trace amounts in air. Thus, the O_2, CO_2, and N_2 concentrations given by a mass spectrometer are concentrations relative to a dry gas whether or not water vapor was a component of the originally sampled gas.

Carbon dioxide analyzers measure absorption by CO_2 of appropriate wavelengths of infrared light. Infrared light is passed through a cell containing the gas to be measured, and the amount of light transmitted is compared with a reference value. Absorption is proportional to the fractional CO_2 concentration. The measurement cell must be kept clean and free of water condensation.

Oxygen analyzers use several different principles. The paramagnetic analyzer measures the change in a magnetic field introduced by differences in oxygen concentration. Because other respiratory gases have little paramagnetic susceptibility, these will not affect the magnetic field. The more commonly used electrochemical O_2 analyzer depends on chemical reactions between O_2 and a substrate that generates a small electrical current. This current is proportional to the rate of O_2 molecules reacting with the substrate and thus to the concentration of O_2.

These latter CO_2 and O_2 analyzers measure partial pressure of the gas and are affected by water vapor, resistances in the sampling systems, and changes in barometric pressure and altitude. Thus, for a given fractional concentration of gas, changes in any of these conditions at the sensor location will erroneously result in different measured gas fractions. Because the sample flow rate delivering gas to the analyzer is held constant, a change in sampling site pressure may result from changes in resistance of the delivery tubing. Using a high-pressure suction pump and a large resistance in the connection between the analyzer and the pump minimizes this effect. Care must be taken to ensure that sample tube resistance is identical during calibration and patient measurement, and that water condensation, saliva, or foreign bodies are not trapped in the delivery tubing.

Both CO_2 and O_2 analyzers report the fraction of CO_2 or O_2 in the total gas, including any water vapor present. This is especially important to consider during calibration because ambient air contains water vapor. Expired gas is saturated with water vapor at the lowest temperature that it reaches before reaching the gas analyzers. Because temperature determines the partial pressure of water in a saturated gas, this temperature must be accurately known or estimated if expired CO_2 and O_2 are to be accurately determined. Tubing has been developed that allows equilibration of the water vapor partial pressure within the tube with that of ambient air, so that the water vapor partial pressure of the gas delivered to the analyzer is equal to that of ambient air and is not influenced by the temperature of the gas at the point of sampling. Additional discussion of the significance of water vapor can be found in Appendix C.

Ergometers: Treadmills and Cycles

Treadmill

Treadmills allow subjects to walk, jog, or run at measured speeds and grades of incline. A variety of protocols for increasing work performed have been designed, and both low and high work rates may be obtained. Treadmills have some advantages over cycle ergometers. A subject performing on a treadmill generally has a peak $\dot{V}O_2$ approximately 5% to 10% higher than on a cycle ergometer, and some subjects and patients are simply not able to cycle because of problems of coordination or inexperience. On the other hand, treadmills may introduce movement artifacts in measurement of ventilation, pulmonary gas exchange, and blood pressure.

Of greatest importance is the fact that if the subject holds on to any part of the treadmill, such as a hand railing, or to the arm of a technician or physician, the amount of work performed by the patient is reduced, thus interfering with the accurate determination of the $\dot{V}O_2$–work rate relationship and work efficiency.

Cycle Ergometer

Cycle ergometers enable a precise estimation of the work rate. Leg cycling may be performed sitting or supine. Advantages of the cycle ergometer over the treadmill include the ability to vary the work rate in step, incremental, or ramp fashion; the ability to determine work efficiency; potentially greater safety because the subject is supported at all times; and less movement artifact on measurements. Some patients may not be able to pedal the cycle because of lack of coordination and experience, or tolerate the seat discomfort during a long study.

When the patient is seated in the upright position, seat height should be adjusted so that the leg is almost completely extended at the lowest point of the pedaling cycle. It is useful to record the seat height in the subject's

records so future studies may be done identically. Subjects should be asked to wear shoes suitable for the types of pedals on the cycle. Toe clips may or may not be used, as desired. Because subjects should cycle at a relatively constant rate, a metronome or tachometer should be used to assist subjects' pedaling speed.

Two types of cycle ergometers are in general use. Mechanically braked devices use an adjustable brake to increase or decrease contact of a friction belt with a moving flywheel attached to the pedals. The work rate achieved is proportional to the cycling frequency or speed of the flywheel, but a particular work rate is only achieved if the subject cycles within a narrow range of pedaling rate. An electrically braked cycle ergometer uses a variable electromagnetic field to produce a resistance to pedaling that varies with flywheel speed, changing the resistance to cycling to maintain work rate at the set level regardless of pedaling speed. A work rate set on this type of cycle ergometer is thereby present over a wide range of cycling speeds. The work rate on the electrically braked devices may be set by a remote controller, or it may be adjusted automatically by a digital computer controller.

When a subject pedals on the cycle with no resistance added or "unloaded," some work is obviously being performed. In addition to the work rate necessary to move the legs, the work rate needed to keep the cycle flywheel in motion can be 5 to 15 W for electromagnetically braked ergometers, but it may be as much as 20 to 30 W for mechanically braked cycle ergometers. Particularly for the latter, it will vary considerably with pedaling rate. This low work rate may exceed the maximal capacity of some severely limited patients. Manufacturer's specifications may provide information on the work rate of unloaded cycling, but users should make this determination for themselves. We have used a special protocol (see "Selecting the Rate of Work Rate Increase" later in this chapter) that uses an accessory motor attached to the cycle flywheel that keeps it spinning at a rate sufficient to remove the inertial energy needed by the subject to start cycling while simultaneously minimizing the "unloaded" work rate (virtually zero watts above the power output needed for moving the legs at the assigned pedaling rate).

Cycle versus Treadmill

Whether the treadmill or the cycle ergometer is the preferable mode of exercise for exercise testing has been a subject of considerable debate (Table 6.1). As noted before, in most subjects and patients, peak $\dot{V}O_2$, peak O_2 pulse, and anaerobic threshold (*AT*) values are generally higher on the treadmill than cycle by approximately 10%,[43] although peak heart rate (HR) and peak ventilation are similar. The treadmill has been in common use in the United States for decades. It allows one to exercise most ambulatory patients except those who are severely dyspneic, uncoordinated, or confused, or those who have significant lower extremity musculoskeletal disease. Length of stride as speed or grade is changed, shift of center of gravity, and change from walking to jogging all can affect the patient's metabolic requirement. Repeated experience on the treadmill may lead to some increase in the efficiency of walking.

None of our patients have been injured using the cycle or treadmill, but we believe that the cycle is safer for those patients who are less coordinated or who have cardiovascular disease. Even the most athletic patients require several minutes of practice in starting and ending the treadmill exercise before beginning measurement.

Table 6.1

Comparison of Treadmill and Cycle Ergometers for Exercise Testing

Feature	Treadmill	Cycle
Higher peak $\dot{V}O_2$ and peak O_2 pulse	+	
Similar peak heart rate and peak $\dot{V}E$	+	+
Familiarity of exercise	++	+
Safety (better patient control, fewer injuries)		+
Quantitation of external work	– –	+
Freedom from artifacts in ECG, airflow, and pressure tracing	– –	++
Ease of obtaining arterial blood specimens	– –	++
Patients with pacemakers	++	
Quantifying hemoglobin desaturation with COPD	++	+

More important advantage (++) or disadvantage (– –); less important advantage (+) or disadvantage (–).
ECG, electrocardiogram; COPD, chronic obstructive pulmonary disease.

Although injuries are rarely reported, careful surveillance is necessary. Because patients can lose their balance on the moving belts, it is wise to have additional help immediately available on the sideboard of the treadmill, particularly for elderly patients. With the cycle, the subject can stop exercise on his or her own volition, independent of the examiner's action, as soon as he or she feels symptomatic to the point that he or she wishes to stop exercise. With the treadmill, the patient must signal the examiner, and then the examiner must respond by turning off the treadmill. Thus, stopping the exercise is dependent not only on the patient but also on the reaction time of the examiner controlling the treadmill switch.

Probably, the greatest disadvantage of the treadmill is the uncertainty of accurately quantifying work rate. This is because any connection between the patient and the treadmill, except that between the patient's shoes and the treadmill belt, decreases the expected energy requirement for body movement at that grade and speed. Thus, railings, arm boards, mouthpieces, blood pressure measuring devices, and steadying hands all have the potential to reduce the patient's actual work rate. Therefore, for treadmill exercise, we only allow patients to touch the back of their hand against the handrail for balance; we do not allow the subject to grasp or hold on to the handrails and try to minimize the stabilizing effect of holding the arm when taking blood pressures.

Because there is less arm and torso movement on the cycle than on the treadmill, one finds fewer artifacts in ventilatory and circulatory measurements. Also, obtaining blood samples can be done with greater ease on the cycle.

There are two important clinical situations in which treadmill testing is advantageous. In patients who have pacemakers and are dependent on their pacemakers for increases in HR and cardiac output in order to increase their ability to exercise, the cycle may be a poor exercise instrument. As most pacemakers respond to forward and backward movement (of the pacemaker) to measure metabolic requirements and are not influenced by ventilatory movements, patients with pacemakers and nodal dysfunction usually do not increase their HR appropriately during exercise on a stationary cycle ergometer. Therefore, during incremental exercise on a cycle, the pacemaker may continue to cause the ventricles to beat at a constant slow or resting rate until the patient's dyspnea becomes intense. In such cases, the patient may stop exercise at a low work rate and low HR but with severe dyspnea and marked decrease in end-tidal CO_2 values. When exercising on a treadmill, the same patient may reach an *AT* and $\dot{V}O_2$ approximately twice that of the values obtained on the cycle because of the increased shoulder and torso movement and consequent increase in HR by the pacemaker sensors due to the movements of walking. In some patients with pacemakers, even higher metabolic requirements with higher HR, *AT*, and peak $\dot{V}O_2$ values are reached by having the patient walk as fast as possible on a level surface or by increasing speed rather than grade and speed on a treadmill.

The other situation favoring the treadmill as an ergometer relates to identifying and quantifying the degree of oxyhemoglobin desaturation that may occur during exercise in patients with significant chronic obstructive pulmonary disease (COPD). Hsia et al.[45] compared the cycle to the treadmill using linear protocols increasing work rate at similar rates in 16 patients with COPD. With the treadmill, they found similar exercise times, peak work rates, and peak $\dot{V}E$, but significantly higher peak $\dot{V}O_2$, peak $\dot{V}CO_2$, *AT*/peak $\dot{V}O_2$, and peak $PETCO_2$ with significantly lower peak respiratory exchange ratio (R), peak $PETO_2$, peak $\dot{V}E/\dot{V}CO_2$, and end-exercise SpO_2. Importantly, during more moderate intensity exercise on the treadmill, the $\dot{V}E/\dot{V}CO_2$ values were similar, but $\dot{V}E/\dot{V}O_2$, R, SpO_2, and $PETO_2$ were significantly lower. They considered the importance of R in the alveolar air equation ($PAO_2 = PIO_2 - PACO_2/R$) and logically suggested that the smaller muscle mass utilized in cycle exercise rather than treadmill exercise to accomplish the same amount of work led, with the cycle, to quicker lactic acidemia, higher $\dot{V}CO_2$ and $\dot{V}E$, similar $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, and $PETCO_2$, but necessarily higher R, $PETO_2$, PAO_2, PaO_2, and SpO_2 values. Thus, with the treadmill, the lesser acidenia, lesser $\dot{V}CO_2$, $\dot{V}E$, R, $PETO_2$, PAO_2, PaO_2, and SpO_2 values at the same work rates cause earlier and significantly lower arterial saturation. Thus, when testing for the severity of oxyhemoglobin desaturation that might occur with exercise in COPD, the treadmill is the preferred ergometer. This study also explains the mechanism why walking tests are likely to lead to lower SpO_2 values than cycle tests.

"Seat pain" can be a problem with prolonged repeated testing, but it is uncommon with the short clinical protocols described herein. In agreement with Astrand,[4] we prefer the cycle to the treadmill for ordinary clinical testing because we may better quantify external work rate and thereby establish the patient's work rate–$\dot{V}O_2$ relationship, a critical measurement in assessing cardiovascular function. Obtaining a linear work rate–predictable gas exchange response is more difficult and variable from subject to subject for the treadmill.

Work and Work Rate (Power)

In basic physical units, force (kg-m/sec^2 or newton) equals mass (kg) times acceleration (m/sec^2). When this force is applied over a distance, work is performed. Thus, work (kg-m^2/second^2 or newton-m or joule) equals force (kg-m/second^2 or newton) times distance (m). However, we are most often interested in the rate of work or power, which equals work (kg-m^2/second^2 or newton-m or joule) per second. The unit of power is the watt, and 1 W is defined as 1 joule/second = 1 newton-m/second = 1 kg-m^2/second^3.

During exercise against the resistance of a cycle ergometer, the work rate is the distance traveled by a point on the circumference of the wheel × the rotational frequency of the flywheel × the restraining force. This restraining force can be expressed as newtons or, commonly, as kiloponds (kp), where 1 kp = 1 kg × 9.81 m/second^2. In practice, cycle ergometer work rate (power) is expressed as watts or kp-m/minute. To convert from kp-m/minute to W, divide the former by 6.12. For example, a work rate of 612 kp-m/minute equals 100 W.

Electrocardiogram and Systemic Blood Pressure

Exercise Electrocardiogram

Silver or silver chloride electrocardiogram (ECG) electrodes with circumferential adhesive provide good electrical contact and minimize movement artifacts. These are similar to those used in the intensive care unit (ICU) for ECG monitoring. The skin is shaved if necessary and is rubbed with alcohol before the patches are applied on areas of the body that will not be subject to great motion during exercise. A net vest may reduce artifacts due to movement.

We use 12-lead ECGs for all patients, as shown in Figure 6.2. The arm electrodes are placed on the back above the scapulae; the leg electrodes are placed on the low back above the iliac crests to minimize movement artifact. The chest electrodes (V_1-V_6) are positioned in standard locations on the anterolateral chest. Some systems require additional leads for separate transmission of the HR signal to the computer. Commercial systems allow computer processing of summarized signals to reduce motion artifacts. However, if the signals are noisy, we record 12-lead ECGs at least every minute so that HR are accurately known throughout the study.

Systemic Blood Pressure

Blood pressure should be measured frequently during exercise to be aware of extreme hypertension or to detect impending hypotension. Blood pressure can also be measured and recorded using several commercial devices: mechanically controlled or automated inflatable cuffs and auscultation, or pressure transducers placed over the radial artery. Such devices should be validated against sphygmomanometer measurements made in the opposite arm. Indwelling arterial catheters allow nearly continuous direct measurement of systemic arterial blood pressure and wave contours and afford optimal patient safety. The pressure transducer should be located at the level of the left atrium (approximately the fourth intercostal space at the midaxillary line in the upright position) and the transducer carefully calibrated. More commonly, blood pressure is measured with an anaeroid manometer, inflatable arm cuff, and auscultation.

Oximetry, Blood Sampling, and Arterial Catheters

Valid measurements of Pa_{O_2}, Pa_{CO_2}, or pH for calculation or measurement of Sa_{O_2}, $P(A-a)_{O_2}$, $P(a-ET)_{CO_2}$, or V_D/V_T are very useful for the interpretation of clinical exercise tests. However, on many occasions, correct diagnoses and interpretations can be made using noninvasive measurements.

Pulse Oximetry

Pulse oximetry estimates arterial blood oxygen saturation using pulsatile changes in light absorption. Since the late 1970s, the principle of pulse oximetry has been widely used.[24] This technique estimates arterial oxygen saturation derived from a combination of spectrophotometry and pulse plethysmography. These devices use two wavelengths of light produced by light-emitting diodes, one in the red and one in the infrared spectrum, and a detector that measures transmitted or reflected light from the ear lobe, fingertip, or forehead. Differential absorption of light at these two wavelengths provides enough information to determine the ratio of oxyhemoglobin to

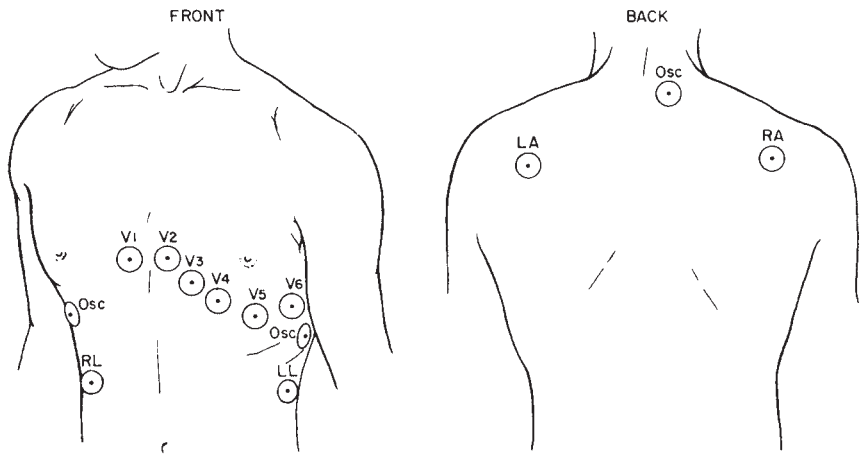

FIGURE 6.2. Electrocardiographic lead placement for upright ergometry. The V_1 and V_2 electrodes are placed more caudad than usually done for supine tracings, whereas V_3, V_4, V_5, and V_6 are in their usual locations. The arm electrodes (*LA* and *RA*) are placed posterior to the shoulders, whereas the leg electrodes (*LL* and *RL*) are placed anterolaterally near the lower rib margins. The three oscilloscope (*Osc*) electrodes are placed separately to minimize electrical interference.

total hemoglobin, assuming that all the pulsatile change is due to the effects of arterial blood. Pulse oximetry is theoretically independent of skin pigmentation and the thickness of the ear lobe or finger; however, some studies have shown that dark skin pigmentation may affect results.[79,96]

Some newer pulse oximeters use eight wavelengths for analysis and detection and thus can now accurately distinguish carboxyhemoglobin and methemoglobin, as well as reduced and oxyhemoglobin.[9] In general, pulse oximetry becomes less accurate when oxygen saturation is less than 75%.[24]

During exercise, movement artifact and stray incidental light may interfere with pulse oximeter accuracy. Although some studies have found acceptable accuracy of pulse oximeters during exercise,[66,70,79,96] Hansen and Casaburi[44] have shown that overestimation and underestimation of arterial blood oxygen saturation may occur near the patient's maximum work rate. Reasons for this may include dependence of the pulse oximeter on sufficient blood flow to the vascular bed measured, a change in the shape of the arterial pulse waveform, a change in empirically determined calibration factors, movement artifact, or other problems. Newer generation pulse oximeters have improved algorithms that allow the devices to cope better with motion artifacts, reduced perfusion, and changes in pulsatile waveforms. These have been tested in critically ill patients and to a lesser extent in the exercise laboratory.[41,93] Fewer motion artifacts may be encountered if a reflectance oximeter probe is placed on the forehead[93] or other less vigorously moving part of the body.

The major disadvantage of pulse oximetry is that arterial oxyhemoglobin saturation rather than arterial P_{O_2} is measured, and that dead space ventilation cannot be validly calculated because Pa_{CO_2} is not measured. Thus, although the correlation between measured arterial O_2 saturation and pulse oximetry O_2 saturation is good, significant decreases in Pa_{O_2} when above 60 mm Hg result in only small decreases in O_2 saturation. On occasions when a determination regarding O_2 therapy is needed, direct Pa_{O_2} measurements may be necessary. In patients with left heart disease, declines in Sp_{O_2} may occur near end-exercise. If such a decline is accompanied by declining blood pressure, light headedness, or plateaus in $\dot{V}_{O_2}$ or O_2 pulse, the decline in Sp_{O_2} can usually be attributed to poor perfusion of the oximeter. On some occasions, blood gas measurements will be necessary for accurate diagnoses.

Single Samples of Arterial Blood

Arterial blood samples allow direct measurement of Sa_{O_2}, Pa_{O_2}, Pa_{CO_2}, pH, lactate, V_D/V_T, $P(a-ET)_{CO_2}$, and other important values. Often, a single sample of arterial blood is obtained during an exercise test to assess blood gases. If this is done, the sample must be obtained before the end of the exercise rather than during recovery because rapid changes in Pa_{O_2} occur immediately when the patient begins to recover from exercise.[38,61,71] Each sample should be drawn over a specific 10- to 20-second period, so that it can be well matched with concurrent gas exchange measurements involving several breaths. The radial artery is the more common site for a single sample; local anesthesia to that site administered before exercise reduces patient discomfort.

Some investigators use free-flowing ear capillary blood or heated hand vein blood as a substitute for arterial blood. Blood values from these sites are likely to approximate arterial P_{CO_2} values for measurement of V_D/V_T but are less likely to approximate arterial P_{O_2} values.

Systemic Arterial Catheter

An indwelling arterial catheter makes repeated sampling of arterial blood for blood gases simple and fast, and it provides continuous monitoring of blood pressure during exercise as well. The most common insertion sites are the brachial and radial arteries, and the same kinds of small-bore catheters used in the ICU for arterial catheterization can be used. The radial artery site has the theoretic advantage that the ulnar artery can supply blood to the hand if the radial artery is blocked, whereas the brachial artery is the sole blood supply of the lower arm. With meticulous care, however, we have never had a serious complication of brachial artery catheterization in several thousand insertions over a 30-year period. A disadvantage of the radial artery site is that it may interfere with gripping of the cycle ergometer handlebars; in addition, referring direct blood pressure measurements to the left atrial level may be more difficult. Figure 6.3 demonstrates the brachial artery catheter in place, and Appendix D describes its insertion.

Arterial punctures and catheterization are rarely complicated by bleeding, arterial spasm, distal arterial thromboembolism, thrombosis, infection, or by significant pain or discomfort. Most frequently, subjects complain of mild discomfort and discoloration from bleeding following puncture. Arterial catheters should be used with special care or avoided in patients with known peripheral arterial disease and in patients with bleeding disorders.

Free-Flowing Ear Capillary Blood

Some investigators and clinicians use free-flowing ear capillary blood[57] as a substitute for arterial blood. When such blood is utilized, it is important that the blood be free-flowing into the receiving capillary tube. The differences between concurrently collected ear capillary and arterial blood are both technique and exercise-intensity dependent. Therefore, it would be desirable for sites that use ear capillary blood to make some simultaneous capillary and arterial blood measures during rest and exercise to determine the pH, P_{CO_2}, and P_{O_2} differences at their site. In optimal circumstances, there are trivial differences in

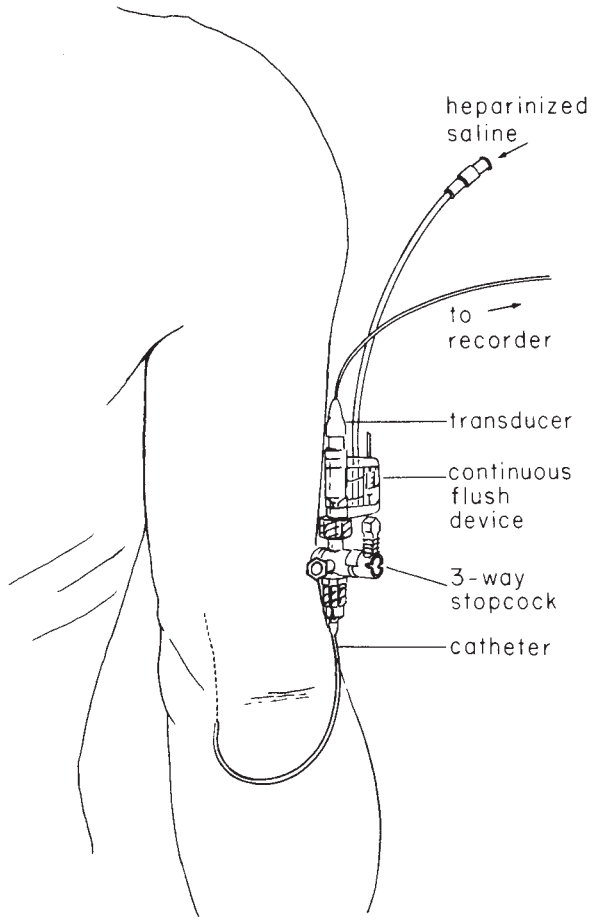

FIGURE 6.3. Brachial artery catheter placement. A 25-cm polyvinyl catheter has been placed percutaneously in the left brachial artery. The dressings have been removed to show catheter placement. The hub of the catheter connects to a continuous-flush device, a threeway stopcock, and a transducer, the last located parallel to the fourth intercostal space in the midclavicular line (at the midatrial level in the sitting position).

pH values (<0.01 units), minor differences in P_{CO_2} values (1 to 2 mm Hg higher in capillary samples), and considerable differences in P_{O_2} values (5 to 10 mm Hg lower in capillary samples with Sa_{O_2} >90%). Thus, these values should be used cautiously in calculating and interpreting values of $P(a - ET)_{CO_2}$, VD/VT, and $P(A - a)_{O_2}$.

Pulmonary Artery Catheter

For some patients, a pulmonary artery (PA) catheter can add valuable information during exercise testing. For example, it may be useful in selected patients with suspected primary or secondary pulmonary hypertension in whom resting PA pressures are borderline elevated. But because of the failure to recruit pulmonary capillary bed during exercise in patients with a pulmonary vasculopathy, the PA pressure can increase strikingly even with a relatively small increase in blood flow induced by exercise. Additionally, PA pressure, PA wedge pressure, mixed venous blood gases, and cardiac output can be measured.

The Swan-Ganz PA catheter is balloon tipped and flow directed, and a physician can pass it through a large vein in the arm through the right atrium, right ventricle, and into the PA with or without fluoroscopic guidance. Because arrhythmias and heart block potentially occur during placement, insertion should be done only with ECG monitoring and appropriate resuscitation equipment and medications standing by, if needed. For pressure measurements, a calibrated transducer and recorder are used. During exercise, especially with patients with lung disease, large swings in intrathoracic pressure with respiration may be transmitted to the PA and wedge pressures, and pressure measurements will be subject to large variation with breathing. Intravascular pressures at end exhalation are selected by convention and are usually most relevant. Blood samples can be drawn from the PA distal port to be analyzed for mixed venous P_{O_2} and O_2 content needed for the calculation of cardiac output using the Fick equation, or calculation of venous admixture.

Cardiac output can also be determined by thermodilution—that is, by rapidly injecting a bolus of isotonic fluid (usually 5% dextrose in water) of known volume, temperature (usually 0° C), specific heat, and specific gravity into the right atrial port of the PA catheter and measuring the temperature change with a thermistor or temperature sensor at the catheter tip in the PA. The temperature change downstream reflects the volume of dilution of the bolus, and cardiac output can be calculated using an automated system. The integral of temperature over time is inversely proportional to cardiac output. Stetz et al.[81] reviewed several studies and concluded that values of cardiac output determined by thermodilution in catheterization laboratories and ICUs were of comparable accuracy to those determined by Fick or dye-dilution methods. These authors suggested, however, that a 20% to 26% difference in cardiac output should be found before concluding that two single determinations were different. Advantages of thermodilution include safety, speed, and repeatability.

Disadvantages of using a PA catheter include increased risks, costs, and preparation time. Uncommon complications can include arrhythmia, heart block, bleeding, perforation of the vein being catheterized or of the right ventricle or PA, and infections. Under specific circumstances, however, the benefits gained from the diagnoses obtained from these catheters outweigh the risks.

Data Sampling and Computation

Automated exercise gas exchange systems make intensive use of computers to control data collection, perform

calculations, store results, and display information. The speed and capability of computerized calculations can correct data from nonlinear analyzers and make adjustments for different environmental or subject characteristics. The computer can also be used to control the ergometer using preprogrammed protocols. Many commercial cardiopulmonary exercise testing systems come with a variety of data displays and printed tables and graphs capable of showing the results of exercise testing, similar to those shown in Chapter 10 of this book. These tools serve most needs for clinical cardiopulmonary exercise testing. Systems also allow reports to be customized and data to be transferred to database and spreadsheet applications.

Typically, data sampled from a flowmeter transducer, gas analyzer, pulse oximeter, HR monitor, or other device undergo analog-to-digital conversion under computer control. Accurate calculations require a sufficiently high sampling rate; for most gas exchange data, a sampling rate in the range of 50 to 100 Hz appears to be adequate. This is easily in the range of available analog-to-digital converters and computer systems.

Quality Control, Validation, and Maintenance

Flowmeter validation is essential for confidence in the ability of the device to measure accurately and reproducibly under testing conditions. Large volume syringes of 1 to 4 L that can deliver known inspiratory and expiratory volumes at very slow to very rapid flow rates are commonly used to calibrate flow devices. If the flow signals are further processed by analog or digital means, the results will be subject to the response characteristics and calculation methods of these instruments.[49] Accurate flow integration is documented by constant volumes over the range of gas flows expected to be encountered. The accuracy of flow and volume can also be determined using a calibrated oscillating pump.

Gas analyzers should be checked for accuracy and linearity within the range of needed values. This can be done by using gases of known concentration of O_2 and CO_2. The Scholander and Haldane methods for gas analysis are accurate, but they are also time consuming, tedious, and now uncommonly used.[25] They may be useful for initial calibration of gas analyzers and primary analysis of stored gases used for calibration purposes. Alternatively, gas having O_2 and CO_2 concentrations of acceptable precision can be obtained from a reliable gas supplier. Such high-precision gases are expensive, but such a tank may be kept for years and used only periodically to assay less expensive gases used for day-to-day calibration. After long storage, it is best to roll tanks to avoid gas stratification.

If an analyzer is nonlinear, a calibration curve can be constructed by observing the analyzer output at several gas concentrations.[40] The analyzers should be warmed up for sufficient time to ensure against electrical drift. Once linearity has been established, a two-point calibration can be used. Room air is often used as one calibration point, assuming an O_2 concentration of 20.93% and CO_2 concentration of 0.04%. A calibration gas of approximately 15% O_2, 5% CO_2, and balance N_2 (but whose actual values are accurately known) is appropriate for the second point because these concentrations are near the expected expired gas concentrations.

For the breath-by-breath calculation of $\dot{V}O_2$ and $\dot{V}CO_2$, the gas transport delay time and the response time of each analyzer to the detection of a new gas concentration are important to know. How these play a role in the calculation is further addressed in Appendix C.

Treadmill speed and grade should be routinely checked for accuracy and reproducibility. Grade may be determined by using a plumb line and tape measure. Speed can be accurately determined by using a stopwatch to time the movement of a mark made on the treadmill belt.

Cycle calibration is highly desirable both during initial setup of the laboratory and periodically thereafter. Manufacturers' specifications and calibration procedures should be followed. Commercially available or specially built devices that generate known amounts of power can act as standards for calibration and verification.[23] Other methods have been devised to provide for cycle calibration and validation.[42,73,85]

In the past, systems of analyzers and computers for determination of gas exchange during exercise were developed and assembled in individual laboratories. The first of these to report the requirements for a breath-by-breath system was Beaver et al.[12] This was later modified to a true alveolar breath-by-breath gas exchange system to correct for changes in alveolar volume and gas concentrations.[11] Now, many good commercial exercise systems are available. They should also undergo validation and have periodic monitoring for accuracy and reproducibility of results.

Validation can be performed by simultaneous collection of mixed expired gas while the exercise system is collecting data.[12,83,86] For mixing chamber and breath-by-breath systems, extremes of tidal volume and flow are particularly challenging. It is easiest to collect expired gas during the steady state of constant work exercise, but such validation may not provide evidence of accurate measurement during rapidly changing exercise protocols or when the major focus is on the short-term time course of gas exchange.

A particularly useful device is an automated calibrator that simulates gas exchange at a known and reproducible rate. One type of simulator uses a sinusoidal pump of known volume and measurable frequency to provide an accurate "expired minute ventilation."[47] Gas exchange (O_2 uptake and CO_2 output) is simulated by the introduction of a gas mixture containing 21% CO_2 in N_2 into a reservoir bag that mixes with room air drawn into the gas exchange measurement system by the pump. $\dot{V}O_2$ and $\dot{V}CO_2$ mea-

sured by the system should be equal to 0.21 × the flow rate of the 21% CO_2 in N_2 flowing into the reservoir bag of the pump calibrator. The respiratory gas exchange ratio should equal 1.00; however, adjustment of the exercise system algorithms may be necessary to accommodate the nearly dry room-temperature gas delivered by the calibrator to the gas exchange measuring device that is set up to measure body temperature—saturated expirate. The pump calibrator has been demonstrated to provide an accurate simulation of gas exchange that can be used for validation and for detection of the source of instrument or algorithm error when an erroneous value is detected. In addition, the device is useful for routine periodic checks of reproducibility. If an error (or change) in measured minute ventilation, $\dot{V}O_2$, or $\dot{V}CO_2$ is found, analysis of the differences in the measurements may also suggest the nature of the problem.

An inexpensive and relatively simple way to test the validity of the entire system is for an individual to cycle at two constant mild-to-moderate work intensities, such as 20 W and 70 W, for 6 minutes each. On such tests, the $\dot{V}O_2$ after 3 minutes should be in a steady state and within 5% to 10% of previously measured values (approximately 0.7 L/min for an individual of average size exercising at 20 W and 1.2 L/min at 70 W, with a difference of 0.5 ± 0.05 L/min). Values significantly deviant from prior tests suggest errors in flow, gas analyzer, or delay measurements or errors in ergometer calibration. If the tested individual can control his or her breathing frequency appropriately, there should be less than 5% difference in $\dot{V}O_2$ whether breathing at a frequency of 15, 30, or 60 breaths per minute. This is an excellent test of the validity of transit delay times and the rapidity of gas analyzer responses. Greater variation in $\dot{V}O_2$ values at higher breathing frequencies suggests errors in delay or response times in the gas analyzers.

Many commercial systems have an option to print a listing of the current status of gas analyzers, environmental conditions, calibration gas concentrations, temperature, and other important system variables. These and validation and reproducibility data should be kept in a laboratory notebook for future reference and evidence of change. This information can be helpful in identifying and resolving problems.

PREPARING FOR THE EXERCISE TEST

The objective of a clinical exercise test should be to learn the maximum about the patient's pathophysiological causes of exercise limitation with the greatest accuracy, with the least stress to the patient, and in the shortest period of time. The optimal examination allows the simultaneous evaluation of the adequacy of the muscles, heart, lungs, and the peripheral and pulmonary circulations to meet the gas exchange requirements of exercise. The test should enable the investigator to distinguish disorders in these systems from inadequate effort, obesity, anxiety, or unfitness.

For the differential diagnosis of exercise limitation caused by cardiovascular or respiratory disease, relatively complete gas exchange measurements should be made. Exercise with large muscle groups is needed to stimulate internal respiration sufficiently to stress the cardiovascular and pulmonary systems. Therefore, either a cycle ergometer or a treadmill should be used to stimulate large muscle groups for testing. Isometric exercise is of limited value because it is largely anaerobic, providing little information about the ability of the cardiovascular and respiratory systems to support the energy requirements of exercise. The protocol selected for exercise testing depends on the purpose of the test.

Requesting the Test and Notifying the Patient

We use a preprinted request form for exercise tests. On this form, the referring physician gives us the following information:

1. Patient's name, address, and telephone number
2. Patient's weight, height, gender, and age
3. Tentative diagnosis and the reason for the study
4. Type of test requested and special requirements

Optimally, the exercise test should be discussed with the referring physician so the type of test and the reason for doing it are clear beforehand. In addition, the discussion helps one to decide whether the cycle or treadmill is the preferable form of ergometry, whether an arterial catheter is desired, and whether supplemental O_2 should be given during the exercise test. This is also a time at which the patient's medications, results of previous studies, special needs or limitations, and other details can be discussed. Other important information includes the specific complaints of the patient during exertion and potential risks and contraindications to exercise.

At the time the exercise test is scheduled, the patient is advised to wear comfortable clothes and low-heeled or athletic shoes, adhere to his or her usual medical regimen, eat a light meal 2 or more hours before arrival, and avoid cigarettes and coffee for at least 2 hours. The patient is given a brief description of the exercise test, including how long it will take and what to expect.

The Patient in the Exercise Laboratory

Preliminary Tests

Because spirometric data are used in the final report, the vital capacity (VC), inspiratory capacity (IC), forced expiratory volume in 1 second (FEV_1), and maximal voluntary ventilation (MVV) should be obtained when the patient arrives at the exercise laboratory.[1] In patients with stable obstructive airway disease, recent spirometric

values may be used. The direct MVV is calculated from a 12-second maneuver of rapid and deep breathing; the indirect MVV is calculated by multiplying the FEV_1 by 40.[18] The MVV values are needed for determination of the exercise breathing reserve. In patients with inspiratory obstruction, neuromuscular disorders, and severe obesity, the direct MVV should be used even if it is considerably less than the indirect MVV. In other patients with poor spirometric efforts, the indirect MVV is usually a more reliable measure of ventilatory capacity.

The hemoglobin and carboxyhemoglobin levels should be known or measured and the DLCO measured in those patients with lung disease or dyspnea. An accurate shoeless height and weight should be obtained.

Physician Evaluation

The physician should obtain relevant clinical information from the patient, with particular emphasis on medications, tobacco and recreational drug use, accustomed activity level, and the presence of angina pectoris or other exercise-induced symptoms. The physician should perform a focused examination with particular attention to the heart, lungs, peripheral pulses, and musculoskeletal system. The physician determines the type of exercise test and protocol on the basis of the exercise request, the clinical evaluation, review of the current ECG and other preliminary tests, and any other special considerations.

Informed consent for the exercise test must be obtained. The patient is told what to expect and that he or she will be asked to make a maximal effort (for most studies), but is advised that exercise can be stopped at any time. The patient is advised of potential discomfort and risks associated with the procedure, the kinds of information that will be obtained, and how this may benefit him or her. Finally, the patient is encouraged to ask questions about the testing before giving consent.

Equipment Familiarization

We find it particularly useful to familiarize the patient with the exercise testing equipment before starting the actual test. If the treadmill is used, time is provided for practice trials so the patient can get on and off the moving treadmill belt with confidence. If the cycle is used, the seat height is adjusted so the legs are nearly completely extended when the pedals are at their lowest point.

The mask or mouthpiece and nose clip are tried before the actual test. The patient is advised that it is acceptable to swallow with the mouthpiece in place or moisten the inside of the mouth with the tongue. We explain the importance of having a good seal of the lips around the mouthpiece or the mask about the face.

Ending the Exercise

We advise patients that they are in charge and can stop exercise if they feel distressed. Alternatively, we stop the exercise if we note important abnormalities. Because a mouthpiece or mask interferes with the ability of the patient to communicate verbally in response to questions regarding symptoms, the patient is taught to use the signal "thumbs up" if everything is satisfactory and "thumbs down" if he or she is experiencing any difficulty but does not wish to stop. The patient is advised to point to the site of discomfort (e.g., chest or leg).

Arterial Blood Sampling and Use of Catheter

If the study requires repeated arterial blood sampling, a catheter is inserted into a radial or brachial artery (see Appendix D for detailed description of how to place the catheter).[76] It is important to check radial and ulnar artery pulsations before and after catheter insertion. The catheter is attached to a stopcock and a blood pressure transducer via a continuous-flush device that provides a slow infusion of a heparin-containing solution (10 units/mL). When one uses a brachial artery catheter, the catheter should be long enough (20 to 25 cm) so that its hub can be brought around to the lateral aspect of the lower part of the upper arm (Fig. 6.3). The transducer is positioned on the upper arm at a height corresponding to the fourth interspace of the midclavicular line (midatrial level when the patient is upright). To avoid spurious dilution of the blood specimen with heparin-containing solution, about 0.5 mL of fluid is discarded before collecting each arterial blood sample (usually by letting the blood flow into gauze under arterial pressure before the sampling syringe is connected to the stopcock). Each sample is collected over 10 to 20 seconds so that the gas tensions are representative of the mean arterial value and minimally influenced by respiratory variations in alveolar gas tensions. Immediately after sampling, the catheter lumen is flushed with heparinized saline. We usually sample blood at rest, at the end of 3 minutes of unloaded cycling or lowest-level treadmill exercise, every 2 minutes during the period of increasing work rate, and at 2 minutes of recovery.

After use, the arterial catheter is removed while keeping direct pressure over the puncture site for at least 5 to 10 minutes. When the pressure is removed, the site is inspected carefully for evidence of bleeding. With adequate pressure and observation after removal of the catheter, hematomas can be avoided. With any evidence of extravascular bleeding, pressure is continued for at least another 3 minutes. A light dressing covered with a firm elastic bandage is then applied over the puncture site, and the peripheral pulses are checked. The bandage should not be so tight as to obliterate the radial pulse (in the case of brachial artery punctures) or to make the hand colder than the contralateral hand (in the case of radial artery catheters). The patient is advised not to use that arm for heavy exercise for the next 24 hours. The dressing and elastic bandage can be removed by the patient at home after several hours have elapsed.

After an exercise test with blood sampling, it is advisable to review the blood gas results before discarding any

remaining blood in the sampling syringes. This makes it possible to reanalyze samples in which the results are questionable.

PERFORMING THE EXERCISE TEST

The following sections describe several different protocols that are used for addressing various clinical questions. Most often, we use a maximum (symptom-limited) incremental exercise test on a cycle ergometer; this protocol is described in detail here. It addresses most clinical and fitness issues. However, if the patient is being evaluated for reasons such as detection of exercise-induced bronchospasm, value of oxygen supplementation in exercise, or other reasons, then other protocols may be appropriate.

Incremental Exercise Test to Symptom-Limited Maximum

In this protocol, the patient exercises on a cycle ergometer (or a treadmill) while measurements of gas exchange are made, breath by breath, at rest, during 3 minutes of very low-level exercise, and while the work rate is increased each minute or continuously (ramp pattern). In general, the patient may be encouraged by the technician and physician in attendance to continue as long as he or she feels that he or she is able. Merely telling subjects that they are in control of how long they exercise, but further advising them that it is important for them to exercise to their maximum level, is sufficient for most patients to go to their reproducible peak $\dot{V}O_2$ or the level of exercise at which $\dot{V}O_2$ no longer increases normally at 10 mL/min/W.

Selecting the Rate of Work Rate Increase

We select the rate of work rate increase after considering the patient's history (especially the amount and intensity of his or her daily activity), physical examination (notably obesity and evidence of cardiac or respiratory disease), and pulmonary function evaluation (particularly the FEV_1 and MVV). If we expect the patient to reach a near-normal power output, we estimate the $\dot{V}O_2$ at unloaded pedaling from the patient's body weight and estimate the peak $\dot{V}O_2$ from the patient's age and height. We then calculate the work rate increment necessary to reach the patient's estimated peak $\dot{V}O_2$ in 10 minutes. The steps that we use to approximate the correct increment for the cycle are as follows:

1. $\dot{V}O_2$ unloaded in milliliters per minute = 150 + (6 × weight in kilograms)
2. Peak $\dot{V}O_2$ in milliliters per minute = (height in centimeters − age in years) × 20 for sedentary men and × 14 for sedentary women
3. Work rate increment per minute in watts = (peak $\dot{V}O_2$ in milliliters per minute − $\dot{V}O_2$ unloaded in milliliters per minute)/100

For example, given an apparently healthy sedentary man 180 cm in height, 100 kg in weight, and 50 years of age, his anticipated $\dot{V}O_2$ unloaded in milliliters per minute = 150 + 6 × 100 kg = 750 mL/min; his anticipated peak $\dot{V}O_2$ = (180 − 50) × 20 = 2,600 mL/min. To achieve an incremental test duration of 10 minutes, we would use a work rate increment of (2,600 − 750)/100 = 18.5 W per minute. Practically, we would select an increment of 20 W per minute and expect the test duration to be slightly less than 10 minutes.

As a generality, if there are not other disease states, peak $\dot{V}O_2$ declines slightly less than the decline in FEV_1, or DLCO. For example, in the absence of other diseases, the following are expected:

1. For a decline in FEV_1 or DLCO to above 80% of predicted, we would expect little reduction of the actual versus predicted peak $\dot{V}O_2$.
2. For a decline of either FEV_1 or DLCO to 50% of predicted, we would expect the actual peak $\dot{V}O_2$ to approximate 60% to 70% of normal.
3. For a decline of either FEV_1 or DLCO to 30% of predicted, we would expect the actual peak $\dot{V}O_2$ to approximate 30% to 50% of predicted.

If the patient has resting tachycardia, symptoms suggestive of angina, or evidence of chronic heart failure, we also reduce the expected peak $\dot{V}O_2$, the amount being judged by our pre-exercise assessment of impairment. Ideally, we reduce the size of the work rate increment in an attempt to keep the total incremental exercise time at about 10 minutes. However, in many patients, their disease is so severe that they cannot tolerate incremental exercise for more than a few minutes. Given a choice, however, we would rather overestimate than underestimate the work rate increment. With too large an increment, the test will be too brief, but the patient will recover quickly, an advantage if retesting is necessary. With too small an increment, however, the patient may stop for ambiguous reasons and may feel too fatigued for retesting. At this point, it is important to stress that we do not concern ourselves with hitting the duration of exercise right on the target of 10 minutes. We prefer it shorter rather than longer than the 10 minutes because we are likely to get a more reproducible and easier test for interpretation. For instance, selection of the *AT* will be more discrete. Exercise tests as short as 5 minutes can be satisfactorily interpreted.

When the patient has severe cardiovascular or pulmonary disease or extreme obesity (with extreme obesity, leg cycling at 60 rpm without an added load may require a $\dot{V}O_2$ of 1.0 L/min), we recommend a special protocol in which, after the rest period, the external workload is incremented less rapidly than usual. With this special protocol, for the first 3 minutes of unloaded pedaling, the patient cycles at 20 rpm; for the fourth minute, at 40 rpm; and for the fifth minute, at 60 rpm. Throughout this

portion of the test, an accessory motor attached to the cycle rotates the cycle flywheel at a speed of slightly over 60 rpm so that the exercise performed is truly unloaded exercise—that is, the energy required for just moving the legs. At the sixth minute, the accessory motor is turned off while the patient continues pedaling at 60 rpm, giving a slight load to the cycle. Starting with the seventh minute, the work rate is then increased by 5 to 10 W per minute. This protocol allows the accumulation of more data at a tolerable metabolic rate and frequently allows delineation of very low *AT* values that are otherwise unmeasurable. Using this protocol, we do not ask the patient to cycle smoothly at 20 and 40 rpm.

Resting Measures

A 12-lead ECG is obtained with the patient in the supine position. If an arterial catheter is placed, we obtain a blood sample in the supine and sitting positions, before the patient breathes through the mouthpiece, to determine the effect of the mouthpiece on the breathing pattern and blood gases. After the patient mounts the cycle or treadmill and is made comfortable, a nose clip is placed and checked for leaks, and the mouthpiece is inserted.

HR, breathing frequency (f) or tidal volume (VT), $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$, and their ratios, plus $PETO_2$, $PETCO_2$, and SpO_2 can be displayed or graphed on a monitor every 5 to 10 seconds or so as the data are collected. ECG tracings should also be visible. The measured and calculated variables are plotted after the test, as shown in Chapter 10. With an arterial catheter, arterial blood pressure is recorded continuously and arterial blood is sampled for blood gases, pH, lactate, cooximetry, and hemoglobin values at rest and during exercise. If an arterial catheter is not used, blood pressure is obtained with a pressure cuff. We usually do not require the patient to make special ventilatory manseuvers at rest or during the exercise test because such maneuvers tend to interfere with the collection of discriminating data.

Unloaded Exercise and Cycling Rate

To overcome the inertia of the cycle flywheel with an electromagnetically braked cycle, an accessory motor[46] can be used to rotate the flywheel at a rate of slightly over 60 rpm while the patient's feet are motionless on the pedals. This unloads the cycle and eliminates the inertial force needed to start the flywheel rotating and reach the desired speed. This is particularly helpful for testing patients with limited strength in their legs. At a verbal signal, the patient begins 3 minutes of unloaded pedaling. The patient is advised to look at the rpm meter and to maintain a cycling speed of 60 rpm, or listen to the cadence of a metronome to establish the pedaling speed. After the patient has established the cycling rhythm, the motor controlling the flywheel speed is turned off so that the patient is now controlling the speed of the unloaded flywheel. A 12-lead ECG, blood pressure measurement, and, if the patient has an arterial catheter, a blood sample are obtained near the end of the 3 minutes of unloaded pedaling.

Incremental Exercise

Measurements are continued while the work rate is increased continuously (ramp)[89] or by a uniform amount each minute until the patient is limited by symptoms or the examiner believes that exercise cannot be continued safely (Fig. 6.4). An increment rate is selected depending on the expected performance of the patient. A 12-lead ECG is recorded every 1 or 2 minutes; arterial samples for blood gas and pH measurement are ordinarily obtained every 2 minutes if the patient has an indwelling arterial catheter. The technician and physician work cooperatively in observing the patient's facial expression, checking the blood pressure and ECG recordings for untoward changes and arrhythmia, looking for nose or mouthpiece leaks, observing for signals of distress from the patient, and quietly encouraging the patient to maximize his or her performance. This is done by commenting on the satisfactory nature of the study, as well as encouraging patients to do their best but to stop when they feel that they must. The resistance of the cycle is removed if the patient evidences distress, if there is a fall in systolic or mean blood pressure greater than 10 mm Hg, if a significant arrhythmia develops, if the patient has ST segment depression of 3 mm or greater, or if the patient stops on his or her own volition. The exercise is also terminated if the patient is unable to maintain cycling frequency above 40 to 45 rpm. If practical and indicated, an arterial blood sample is obtained during the last half minute of exercise.

Recovery

We ask the patient to continue to breathe through the mouthpiece during 2 to 3 minutes of recovery. In the immediate postexercise period, the patient is advised to continue to pedal at a slow frequency without a load on the ergometer. This leg movement tends to minimize the precipitous fall in blood pressure and light-headedness that are often experienced with the abrupt decrease in venous return due to lower extremity vasodilatation or arrhythmias that may occur when vigorous exercise is abruptly terminated. If arterial blood is being sampled, a final sample is obtained at 2 minutes of recovery.

Postexercise Questioning and Review

At the conclusion of the test and soon after removal of the mouthpiece (after at least 2 minutes of recovery gas exchange measurements), the physician should question the patient in a nonleading fashion about what symptoms caused him or her to stop exercise. A series of questions

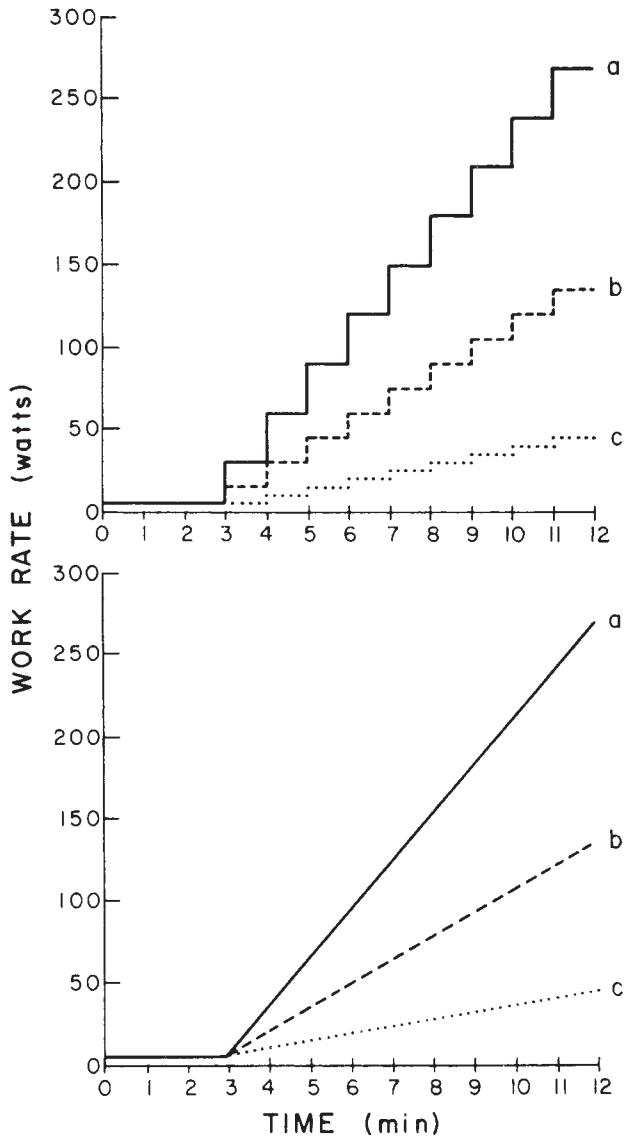

FIGURE 6.4. One-minute incremental (upper) and ramp incremental (lower) protocols for cycle ergometry. In both cases, the subject initially cycles for 3 minutes of unloaded pedaling. In the example shown, the work rate is incremented 30 W (*a*), 15 W (*b*), or 5 W (*c*) per minute depending on the height, age, gender, and health of the subject. The increment is added at the start of each minute for the 1-minute test, whereas the increment is completed at the end of each minute for the ramp test. Larger or intermediate increments can also be used. The cycle is returned to the unloaded setting when the cycling frequency cannot be maintained over 40 rpm or when the physician or subject decides to terminate the incremental exercise.

may be required to assess just what the patient means by his or her limiting symptoms. For example, it is important to differentiate calf from thigh pain and to determine the exact character of any chest discomfort. In particular, it is always worthwhile to find out if the symptoms reproduce the complaints of exertional dyspnea or chest pain or other discomfort experienced by the patient outside the laboratory.

If, on review of the data, it appears that a symptom-limited test was terminated prematurely because of inadequate patient effort, a repeat test after a recovery period of 30 to 45 minutes may be indicated. For instance, if the patient made an insufficient effort, as suggested by the combination of high breathing and HR reserves, a low R, and only a slight fall in arterial bicarbonate, measured directly or estimated from the plotted data, the test bears repeating with greater encouragement from the examiner. In these repeat tests, the reproducibility of the patient's performance should be examined.

Critique of Incremental Tests

Balke and colleagues introduced the use of 1-minute incremental treadmill tests for the study of fitness in a large military population.[6,7] Although Balke initially used a 1% increment in grade per minute with a constant treadmill speed of 3.3 mph, he also used a 2% increment in grade every minute. Several investigators, including Consolazio et al.,[26] Jones,[50] and Spiro,[80] used the cycle ergometer with the work rate incremented an equal amount every minute or half minute. Increments of 8, 15, 17, or 25 W per minute, 10 W per half minute, or 4 W every 15 seconds have been reported.[34] We introduced the use of a continuously incrementing (ramp-pattern) exercise protocol[31,89] and have used it extensively in adults and children.[27]

In comparing the ramp test with 1-, 2-, and 3-minute step increments at the same overall average work rate increase, Zhang et al.[97] have shown that no significant differences were found in the $\dot{V}O_2$max, *AT*, peak $\dot{V}E$, peak HR, $\Delta \dot{V}O_2/\Delta WR$, or exercise duration among the four protocols in healthy subjects. Step patterns in some measures could be seen in the 2- and 3-minute step protocols, however (see Fig. 4.3). Thus, although any of these protocols might be used, either the ramp or the 1-minute incremental test seems practical and preferable for patients because they do not feel sudden increases in work rate.

Several investigators[3,69] have stressed the desirability of adjusting the work rate increment according to the patient's cardiorespiratory status. Tests that are too brief (i.e., with the work rate increased too rapidly) may not allow a sufficient quantity of data to be accumulated. Tests that are too long (i.e., with too small a work rate increase) are likely to be terminated prematurely because of boredom or "seat discomfort." We found that tests in which the incremental part of the protocol is completed between 6 and 12 minutes give the highest peak $\dot{V}O_2$ in normal subjects.[17] Longer or shorter tests are likely to give slightly lower values. We know of no similar study in patients with heart or lung disease; we assume that the findings would be similar in such patients. Therefore, we attempt to select a work rate increment that will result in termination of the incremental part of the exercise test in 8 to 10 minutes, but tests as short as 6 minutes are acceptable.

Some investigators have expressed concern regarding whether the peak $\dot{V}O_2$ is as high in continuous incremental protocols as in discontinuous protocols and whether the highest $\dot{V}O_2$ reached (peak $\dot{V}O_2$) should be identified as the $\dot{V}O_2$max. Taylor et al.[84] defined the $\dot{V}O_2$max from a series of progressively higher constant work rate tests. They defined the $\dot{V}O_2$max as the $\dot{V}O_2$ when an increase in work rate resulted in an increase of $\dot{V}O_2$ of less than 150 mL per minute above the $\dot{V}O_2$ from the previous lower work rate. This criterion is appropriate for tests in fit subjects using large work rate increments, such as a 2.5% grade change at a treadmill speed of 7 mph. In tests featuring a 15 W per minute increase in work rate, however, the rate of increase in $\dot{V}O_2$ is normally only 150 mL per minute. Therefore, at increments of 15 W per minute or less, it is invalid to use the criterion of Taylor et al. to determine whether the peak $\dot{V}O_2$ is indeed the $\dot{V}O_2$max.

A single study[37] reported an approximately 10% lower peak $\dot{V}O_2$ using a continuous rather than a discontinuous graded work rate test; however, the long duration (20 to 30 minutes) of these continuous tests could have accounted for the reduction.[69] In contrast, Maksud and Coutts,[53] Wyndham et al.,[92] and McArdle et al.[54] found no difference in peak $\dot{V}O_2$ measured in continuous incremental tests compared with discontinuous constant work rate treadmill tests. Pollack and colleagues[63] found a plateau in $\dot{V}O_2$ in 59% to 69% of the continuous incremental treadmill tests they administered. We found a similar peak $\dot{V}O_2$ in normal men using a ramp-pattern increase in cycle ergometer tests, whether the increase was 20, 30, or 50 W per minute.[31] Thus, we believe that the $\dot{V}O_2$max can be approximated with continuous incremental protocols of the proper duration.

Using the ramp-pattern test, we also found that the *AT*, time constant for $\dot{V}O_2$, work efficiency, maximum $\dot{V}E$, and maximum HR were comparable to values found with constant work rate tests.[31,89] Because we were concerned that non–steady-state incremental exercise tests might give different values for $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$, $P(A-a)O_2$, $P(a-ET)CO_2$, and HR as compared to steady state, we studied 23 men (11 normal, 9 with obstructive lung disease, and 3 with restrictive lung disease) during steady-state constant work rate and 1-minute incremental exercise tests (Table 6.2).[39] The steady-state exercise $P(A-a)O_2$ values ranged from 1 to 43 mm Hg, and the VD/VT values ranged from 0.12 to 0.44. We found that $\dot{V}CO_2$, $\dot{V}E$, PaO_2, and R were slightly lower during incremental exercise than constant work rate exercise at the same $\dot{V}O_2$. These differences were anticipated and can be fully explained by the differences in kinetics of $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ in incremental versus constant work exercise. The $P(A-a)O_2$, $P(a-ET)CO_2$, $PaCO_2$, $\dot{V}E/\dot{V}CO_2$, and VD/VT values were in close agreement in both protocols for both the normal subjects and the patients, however. Thus, it is possible to make measurements of gas exchange and ventilation–perfusion matching equally well during incremental or steady-state exercise.

With rapid incremental tests, frequent and accurate measurements are needed. Blood pressure and HR are not difficult to measure. Accurate measurement of $\dot{V}E$, $\dot{V}CO_2$, and $\dot{V}O_2$ requires special thought and understanding of the properties of the measuring devices. The reader is referred to Beaver et al.[10,12] and Sue et al.[83] for an analysis of potential errors.

Constant Work Rate Exercise Tests

Exercise tests performed with the patient or subject exercising at a constant work rate may be useful in particular situations. The selection of the appropriate work rate de-

Table 6.2

Effect of Protocol on Measurements of PaO_2, $P(A-a)O_2$, and VD/VT during Cycling at the Same Mean $\dot{V}O_2$ (0.92 ± 0.03 L/min)

		PaO_2, mm Hg		$P(A-a)O_2$, mm Hg		VD/VT	
	N	Incremental[a]	Constant[b]	Incremental	Constant	Incremental	Constant
Normal	11	89	94	14	13	0.26	0.25
Restrictive lung disease	3	87	89	18	21	0.21	0.19
Obstructive lung disease	9	79	83	25	22	0.32	0.32
All subjects	23	85[c]	89	19	17	0.27	0.28

[a]1-minute incremental exercise protocol.
[b]Constant work rate protocol; measurements were made at 6 minutes.
[c]Indicates significant difference between 1-minute incremental and constant work rate test at $p < .05$ by paired t test; other differences are not significantly different.
(Data are from Furuike AN, Sue DY, Hansen JE, et al. Comparison of physiologic dead space/tidal volume ratio and alveolar-arterial PO_2 difference during incremental and constant work exercise. *Am Rev Respir Dis.* 1982;126:579–583.)

pends on the question being addressed and the number of different work rates that are chosen. Constant work rate exercise tests may be helpful in determining $\dot{V}O_2$max or the lactic acidosis threshold, measuring gas exchange kinetics, diagnosing exercise-induced bronchospasm, and assessing the contribution of the carotid bodies to exercise hyperpnea.

Determining $\dot{V}O_2$max

Historically, discontinuous constant work rate tests, each with a large increase in work rate with intervening rest periods, were used to measure $\dot{V}O_2$max.[5] The advantages of determining $\dot{V}O_2$max from progressively greater constant work rate tests are as follows:

1. The higher-intensity work rates selected can be based on the patient's cardiovascular and ventilatory responses to the lower work rate tests.
2. Timed manual bag collection of mixed expired gas for measurement of $\dot{V}CO_2$ and $\dot{V}O_2$ near the end of each exercise does not require rapidly responding gas analyzers.
3. Failure of the $\dot{V}O_2$ to increase despite an increase in work rate provides unequivocal identification of $\dot{V}O_2$max.

The disadvantages of determining $\dot{V}O_2$max from progressively greater constant work rate tests are as follows:

1. The repeated constant work rate tests take considerable time for patient, physician, and technician.
2. These tests are exhausting and may be more likely to result in injury to the patient.
3. Although such tests are often considered steady-state tests, this cannot be true at work rates at or above that necessary to ensure a $\dot{V}O_2$max, and likely at any work rate accompanied by a significant lactic acidosis.

Measuring Gas Exchange Kinetics

Constant work rate tests are ideal for measuring cardiovascular, ventilatory, and gas exchange kinetics. Measurement of these variables, especially $\dot{V}O_2$, during the transition from rest to low-level exercise or between two levels of exercise using breath-by-breath analysis allows measurements of time constants or halftimes of response.[60] Averaging the data obtained from several constant work rate breath-by-breath tests, measured from the start of exercise, may be necessary for adequate precision.[52,90]

Sietsema et al.[77] used such a protocol to demonstrate striking reductions in the $\dot{V}O_2$ increase during the first 20 seconds after exercise onset in patients with cyanotic congenital heart disease. In normal subjects, the magnitude and mean response time (MRT) of $\dot{V}O_2$ correlated well with the fitness (peak $\dot{V}O_2$ per kilogram) of the individual; the lower the peak $\dot{V}O_2$ per kilogram, the longer the MRT for constant work rates of 100 W or higher.[78] Similarly, Ben-Dov et al.[14] demonstrated significantly lower increases in $\dot{V}O_2$ in the first 20 seconds of constant work rate exercise in hyperthyroidism, despite the overall higher metabolic requirement of the disease. At higher constant work rates, Koike et al.[51] demonstrated the lengthening of the $\dot{V}O_2$ time constant as carboxyhemoglobin levels were increased.

Determining Anaerobic Threshold

The measurement of $\dot{V}O_2$ kinetics over a 6-minute period of constant work rate can also be useful. If the *AT* is uncertain after incremental testing, a constant work rate test can be performed at a work level expected to approximate the individual's *AT*. If the work rate turns out to be above the individual's *AT*, the $\dot{V}O_2$ will not plateau by the end of the third minute, but will continue to rise.[91] The degree of rise will be greater the further the work level is above the *AT* and correlates highly with the extent of the developed lactic acidosis (see Figs. 2.54 and 4.27).[20,72] Repeated testing at one or two other constant work rate levels should allow an accurate determination of the *AT*.

Several studies have shown the utility of precisely assessing the *AT* and the $\Delta\dot{V}O_2$ (6 – 3) to disorders in O_2 transport. Casaburi et al.[21] showed the advantage of training patients with chronic obstructive pulmonary disease with constant work rates above rather than below their *AT*s. Koike et al.[51] demonstrated increases in the $\Delta\dot{V}O_2$ (6 – 3) with reductions in hemoglobin availability for transport of O_2, while Zhang et al.[98] showed a positive correlation between the $\Delta\dot{V}O_2$ (6 – 3) and the severity of heart failure in patients with chronic stable heart failure.

Detecting Exercise-Induced Bronchospasm

Although exercise-induced bronchospasm can often be demonstrated after the usual incremental testing in the afflicted individual, it may be more evident after 6 minutes of near-maximal constant load exercise.[29] It is necessary to obtain good baseline measurements of FEV_1 or some other index of airway obstruction immediately before exercise. Most investigators prefer the treadmill to the cycle ergometer for inducing postexercise bronchospasm, although we have used both successfully. To induce postexercise bronchospasm, it is our practice to increase the work rate to approximately 80% of the predicted maximal work rate after a 1-minute warm-up at a lower work rate. The patient inspires dry air from a bag filled from a tank of compressed air rather than room air because, according to current concepts, dry air aids in the induction of bronchospasm and reduces day-to-day variability if repeated tests are necessary.[32] After 6 minutes of heavy exercise, the mouthpiece is immediately removed. Spirometric tracings are obtained as soon as possible and at 3, 6, 10, 15, and 20 minutes after exercise.

Measuring Carotid Body Contribution to Exercise Ventilation

The effect of carotid body input to the medullary respiratory centers can be assessed by altering the PO_2 of the blood reaching the carotid bodies.[88] Normally, if the carotid bodies are contributing significantly to ventilatory drive, a rise in carotid artery P_{O_2} will immediately reduce the carotid body neural outflow and depress ventilation transiently. This can be detected by an immediate fall in $\dot{V}E$, VT, and *f* and a rise in P_{ETCO_2} approximately 6 to 10 seconds after an unobtrusive switch of inspiratory gas from room air to 100% O_2 (see Fig. 4.31). After 1 minute of 100% O_2 breathing, a switch back to room air results in a return to baseline $\dot{V}E$ and P_{ETCO_2} values. Online recording of VT, *f*, and gas concentrations, breath by breath, is desirable.

Because ventilation is less variable during exercise than at rest, we prefer to perform these measurements during constant work rate exercise of moderate intensity. Steady-state levels of $\dot{V}E$ at moderate exercise are usually attained in less than 5 minutes. Thus, the effect of the change in F_{IO_2} can be more clearly detected and quantified during exercise. Maximal inhibitory effect is usually seen with an increase in Pa_{O_2} to 250 mm Hg or more. Usually, with normal arterial O_2 saturation, $\dot{V}E$ will decrease transiently by about 15% during the 1-minute switch to 100% O_2 breathing. If a pneumotachograph is used to determine ventilation, an adjustment must be made in calculating the ventilatory decrease to account for the 11% higher gas viscosity of 100% O_2 than air. The flowmeters of some commercial systems automatically correct for this difference in gas viscosity with changing O_2 concentration. This can be documented by calibrating with a known volume of air and O_2 and determining if there is a difference in recorded volume.

Treadmill Test for Detecting Myocardial Ischemia

Several investigators have developed and popularized incremental treadmill protocols for inducing and detecting ECG changes consistent with myocardial ischemia.

Bruce[15] developed a protocol that begins with 3-minute stages of walking at 1.7 mph at 0%, 5%, or 10% grade (Fig. 6.5C). The 0% and 5% grades are omitted in more fit individuals. Thereafter, the grade is incremented 2% every 3 minutes and the speed is incremented 0.8 mph every 3 minutes until the treadmill reaches 18% grade and 5 mph. After this, the speed is increased by 0.5 mph every 3 minutes.

Ellestad[33] uses seven periods, each of 2 or 3 minutes' duration, at progressively increasing speeds of 1.7, 3, 4, 5, 6, 7, and 8 mph (Fig. 6.5E). The grade is 10% for the first four periods, with durations of 3, 2, 2, and 3 minutes, respectively, and 15% grade for the last three periods, each of 2 minutes' duration.

Patterson et al.[62] use 10 exercise periods of 3 minutes' duration, each separated by rest periods of 3 minutes (Fig. 6.5A). The grade and speed of each period are as follows: 0% and 1 mph; 0% and 1.5 mph; 0% and 2 mph; 3.5% and 2 mph; 7% and 2 mph; 5% and 3 mph; 7.5% and 3 mph; 10% and 12.5% and 3 mph; and 15% and 3 mph.

In each of these treadmill protocols, blood pressure is measured and a multiple-lead ECG is recorded at each work rate and during recovery. The patient is carefully observed, and the test is terminated at the physician's discretion (e.g., for decline in blood pressure, significant ventricular arrhythmia, progressive ST segment changes, or attainment of a given HR) or by the patient's symptoms.

Itoh et al.[48] and Belardinelli et al.[13] have advanced the application of the exercise ECG in diagnosing myocardial ischemia by combining it with gas exchange measurements. They found that accompanying changes in the ECG, the $\dot{V}O_2$–work rate relationship becomes more shallow, providing evidence of myocardial dyskinesis.

Critique

These treadmill tests have the advantage of extensive clinical use. A survey in 1977 concluded that the complication rate for such exercise stress testing was 3.6 myocardial infarctions, 4.8 serious arrhythmias, and 0.5 deaths per 10,000 tests.[82] In this survey, the treadmill was the ergometer used most often (71%), and the favorite protocol (65%) was that of Bruce.[15]

The peak $\dot{V}O_2$ is generally 5% to 11% higher with treadmill as compared with cycle ergometer testing,[12] whereas maximum HR is similar. As usually performed, $\dot{V}E$, breathing pattern, $\dot{V}O_2$, and gas exchange are not measured during these tests, so other important information on cardiovascular and pulmonary system function is not available. Bruce et al.[16] have shown a high correlation of maximum $\dot{V}O_2$ and duration of treadmill exercise in their normal population.[16] Nevertheless, it is invalid to consider the duration of exercise a measure of peak $\dot{V}O_2$ in patients suspected of having cardiovascular disease. The unequal duration of increment and variability in increment size are disadvantages of these tests, although interpretation is usually not based on measurements of $\dot{V}O_2$. In addition, HR itself is a poor measure of exercise intensity in many patients with heart disease. Administration of β-adrenergic blocking drugs also modifies the HR–work rate relationship and must be taken into account when interpreting the results of exercise tests.

Rather than using the foregoing protocol for treadmill testing, Jones[50] and Buchfuhrer et al.[17] have used constant treadmill speed and have incremented the grade by a constant amount each minute for the entire study. After 3 minutes of warm-up at zero grade and a comfortable walking speed (which may range from 0.8

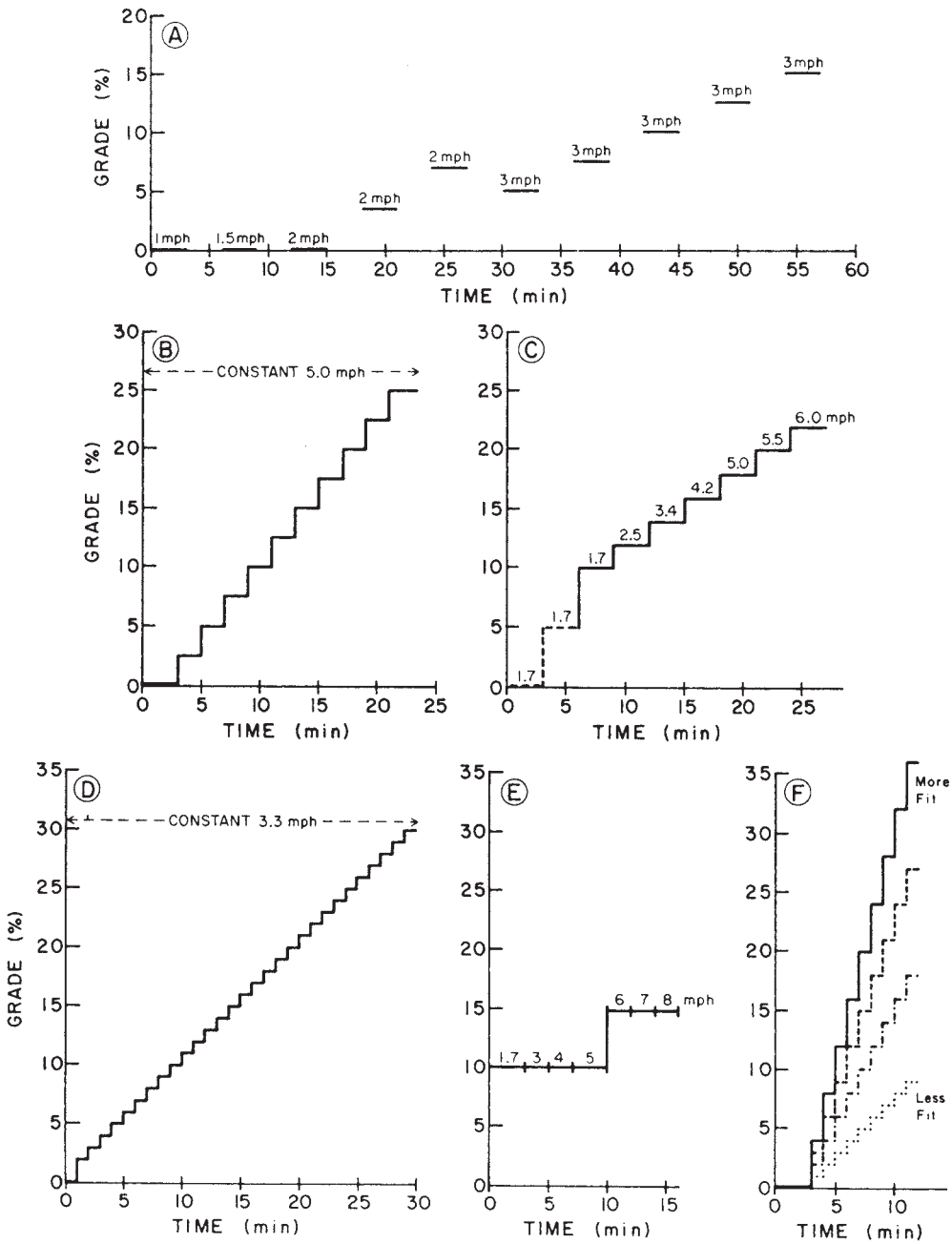

FIGURE 6.5. Several treadmill protocols. **A**: Naughton protocol. Three-minute exercise periods of increasing work rate alternate with 3-minute rest periods. The exercise periods vary in grade and speed. **B**: Astrand protocol. The speed is constant at 5 mph. After 3 minutes at 0% grade, the grade is increased 2.5% every 2 minutes. **C**: Bruce protocol. Grade and speed are changed every 3 minutes. The 0% and 5% grades are omitted in healthier subjects. **D**: Balke protocol. After 1 minute at 0% grade and 1 minute at 2% grade, the grade is increased 1% per minute, all at a speed of 3.3 mph. **E**: Ellestad protocol. The initial grade is 10% and the later grade is 15%, while the speed is increased every 2 or 3 minutes. **F**: Harbor-UCLA protocol. After 3 minutes of walking at a comfortable speed, the grade is increased at a constant preselected amount each minute—1%, 2%, or 3%—so that the subject reaches his or her peak $\dot{V}O_2$ in approximately 10 minutes.

to 4.5 mph, depending on our assessment of the patient's fitness), we use a constant grade increment of 1%, 2%, or 3% each minute to the patient's maximum tolerance. We scale speed and grade so the test will end approximately 10 minutes after we begin to increment the treadmill grade (Fig. 6.4F).

We have successfully used protocols recommended by Porszasz et al.[65] designed to linearize the increase in work rate. These protocols initially use a slower speed and grade for the 3 minutes of warm-up, followed by a ramp or minute-by-minute increment in either speed or grade (or both) to maximal toleration. We, of course, also make measurements of $\dot{V}E$, $\dot{V}CO_2$, and $\dot{V}O_2$. Following an initial delay of about 45 seconds after the increment begins, the aforementioned protocols give a relatively linear increase in $\dot{V}O_2$ in normal subjects. The additional measurements allow us to calculate values such as peak $\dot{V}O_2$, *AT*, R, peak $\dot{V}E/MVV$, $\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, and O_2 pulse, thus adding considerable insight into gas exchange, ventilatory, and cardiovascular function.

Arm Ergometry

Arm exercise protocols similar to those for lower extremity exercise are usually done because of dysfunction of the lower extremities. The usual technique is to use

a converted cycle ergometer with the axle placed at or below the level of the shoulders while the subject sits or stands and moves the pedals so the arms are alternately fully extended. The most common frequency is 50 rpm. Occasionally, upper extremity exercise is performed using wheelchair wheels coupled to a cycle ergometer or by rowing, paddling, or swimming. These modes may be particularly useful for paraplegics, oarsmen, or athletes. To obtain maximal cardiovascular and respiratory stress, arm cycling must be done concurrently with lower extremity exercise.

If the person performing the test is healthy and has not undergone specific upper extremity training, the peak $\dot{V}O_2$ for arm cycling will approximate 50% to 70% of that for leg cycling.[8,19,30,87] The *AT* for arm cycling for most healthy subjects is also lower than that of leg cycling. Maximum $\dot{V}E$ is similarly reduced, whereas maximum HR is only 2% to 12% less than with leg cycle exercise. Thus, the maximum O_2 pulse is less with arm than with leg cycling.

Critique

Although arm cycling exercise has occasional uses, it does not stress the cardiovascular and respiratory systems as much as leg cycling or treadmill exercise. As such, it is a poor substitute when one assesses the cardiovascular and respiratory systems, except when lower extremity exercise is impossible.

Other Tests Suitable for Fitness or Serial Evaluations

A variety of tests have been used to evaluate individuals or groups without attempting to ascertain whether a particular system (e.g., cardiovascular, respiratory, musculoskeletal) or the motivation of the performer is limiting exercise. Such tests are likely to be used for children, young adults, military personnel, or laborers exposed to environmental stress or pollutants (Fig. 6.5B, D). These tests are often considered measures of cardiovascular fitness and may allow division of the population studied into several levels of fitness, but they can also be used to serially evaluate patients with known disorders. Formerly, these tests could be repeated frequently only with simple equipment. Now, gas exchange measurements with telemetry are possible.

Harvard Step Test and Modifications

The original Harvard step test consisted of having the subject step up and down at a uniform rate of 30 steps up per minute onto a platform 20 inches high for a period of 5 minutes, if possible, with measurements of pulse rate for 30 seconds after 1 minute of recovery.[25] Modifications include the following[25,58,59]:

1. The addition of backpacks that add approximately one-third to the subject's weight
2. Reduction in the duration of the test to 3 minutes
3. Reduction in the step height to 17 inches for women
4. Measurement of HR during exercise
5. Change in the time of measurement of recovery pulse
6. Change in test scoring
7. Use of a gradational step in which the height of the platform can be raised 2 cm every minute or 4.5 cm every 2 minutes

600-Yard Run-Walk

The 600-yard run-walk requires that the subject cover a 600-yard level distance in the shortest possible time.[36] He or she may intersperse running with walking but must try to finish as quickly as possible. A properly marked track or football field is suitable. For 87 male university staff and faculty members, time for completion showed a moderately good correlation ($r = 0.644$) with their peak $\dot{V}O_2$ measured by an incremental cycle ergometer test (which ranged from 25 to 50 mL/min/kg).

12-Minute Field Test

In the 12-minute field performance test, the subjects, dressed in running attire, cover as much distance as possible by running or walking. The distance covered was shown to correlate well ($r = 0.897$) with $\dot{V}O_2$max measured during an intermittent incremental treadmill test in 115 military personnel ($\dot{V}O_2$max range of 30 to 60 mL/min/kg).[28]

12-Minute Walk Test

The distance covered in 12 minutes of walking (equivalent to the original 12-minute field test described by Cooper) has been used for assessing disability in patients with chronic bronchitis.[55] Each patient is instructed to cover as much distance as possible on foot in 12 minutes, such as by walking over a marked course in a hospital corridor. The patient is told to try to keep going, but not to be concerned if he or she has to slow down or stop to rest. The aim is for the patient to feel that at the end of the test, he or she could not have covered more ground in the time given. A physician or therapist accompanies the patient, acting as timekeeper and giving encouragement as necessary.

Daily repetitions of the 12-minute test in 12 hospital inpatients on three different days showed a significant improvement in distance on day 2 over day 1, but not on day 3 over day 2.[14] In 35 patients with lung disease, the distance correlated significantly with peak $\dot{V}O_2$ ($r = 0.52$), maximum exercise $\dot{V}E$ ($r = 0.53$), and forced vital capacity ($r = 0.406$), but not with FEV_1 ($r = 0.283$).[55]

6-Minute Walk Test

The 6-minute walk test evolved in the 1980s as a less strenuous test than the 12-minute walk test, suitable for

patients with heart and lung disorders.[2] It is a relatively simple self-paced test useful for measuring the response to interventions in patients with known disease. It requires a flat, hard surface, such as a long indoor hallway at least 100 feet in length, over which the patient travels back and forth as rapidly as he or she can with fixed encouragement by a monitor. Testing should be performed only where a rapid response to an emergency is possible. Patients with unstable angina or recent myocardial infarctions should not be tested.

The distance covered correlates reasonably well with gas exchange measures of peak $\dot{V}O_2$ measured during incremental tests,[56] and even better when the weight of the patient is factored into the distance covered.[22] In a large trial of patients with chronic obstructive pulmonary disease, the distance covered during the tests on the day after the first test improved by 7% ± 15%, indicating a significant learning effect.[74] The test does not discriminate between the different organ systems that may limit activity and is therefore rarely used as a diagnostic test. Several standards have been proposed as a clinically significant increase in walking distance: 54 ± 17 m,[68] 35 ± 6 m,[67] and 31 ± 13 m.[75] Thus, it has been successfully used in evaluating patients with lung resection, pulmonary rehabilitation, heart failure, pulmonary hypertension, cystic fibrosis, peripheral vascular disease, and obstructive lung disease.[2]

PREPARING THE REPORT

In our laboratory, after entry of blood gas and blood pressure values, the computer system produces graphical and tabular displays of the results of the exercise study similar to those shown in Chapter 10. Consistency of format facilitates interpretation. The layout of the nine-panel graphical array allows one to quickly review the cardiovascular and ventilatory systems, ventilation–perfusion relations, and exercise metabolism. The addition of ECG and blood pressure data usually leads to a pathophysiological diagnosis.

The textual report we prepare includes brief summaries of relevant clinical information and medications, specific exercise-related complaints, pulmonary function test results, a brief description of the methods and procedure, a table of key gas exchange variables, and a narrative analysis and interpretation. We also include a glossary of terms found on the report that may be unfamiliar to some referring physicians. Our recommendations regarding information to be included in the final report are listed in Table 6.3.

SUMMARY

Numerous exercise devices, protocols, and physiological measuring systems are available for the safe and economical evaluation of normal individuals, athletes, or patients suspected of having (or known to have) respiratory, cardiovascular, or neuromuscular disease. The specific exercise performed can be tailored to the diagnostic or therapeutic questions being asked and the facilities and technical and professional expertise available. Ordinarily, a maximum amount of information can be obtained by making ventilatory, gas exchange, ECG, blood pressure, and blood gas measurements during a cycle or treadmill test that includes measurements sitting or standing at rest, followed by unloaded cycling or treadmill walking for 3 minutes, further followed by ramp or 1-minute incremental exercise with an increment size enabling the subject to reach his or her maximally tolerated work rate in about 10 minutes, and finally ending in a 2- to 3-minute recovery period. Less frequently, constant work rate tests, arm ergometry, or timed walking tests may be useful.

Table 6.3

Recommendations for Final Report on an Exercise Test Patient

Recommendation for the report	Example
A. Patient and pretest information	
Patient's exercise-related complaint or the limitation being addressed by the exercise test	Patient experiences shortness of breath while walking up hills.
The specific question being addressed by the requested exercise test (often raised by a referring physician)	What is the degree of exercise limitation? Can my patient tolerate a pneumonectomy? Should oxygen be prescribed for my patient during exercise? Has the new medication improved exercise capacity?

Continued

Table 6.3

Recommendations for Final Report on an Exercise Test Patient *(Continued)*

Recommendation for the report	Example
Pertinent clinical information that may be helpful in relating to the interpretation	Type of exercise limitation noted by the patient (fatigue, chest pain, dyspnea) Level of physical activity in a normal day's routine Medications Occupational history
Findings from a focused physical examination	Blood pressure, chest and heart examination Patient's actual height and weight
Results of other studies relevant to exercise capacity, especially if they contribute to developing the interpretation and conclusions	Resting electrocardiograms, chest roentgenograms, pulmonary function tests, echocardiograms
Recent information	Recent food or medications VC, IC, FEV_1, MVV on day of testing
Pretest diagnosis	COPD, coronary artery disease, asthma, claudication
B. Information about the exercise laboratory	
Exercise laboratory equipment	Type of ergometer used, measurements made
Exercise protocol	Progressive or constant work rate Use of oxygen supplementation
Documentation of other procedures performed in the laboratory, if any	Arterial catheter, pulmonary artery catheter, pulse oximetry, electrocardiograms, postexercise spirometry, noninvasive blood pressure measurements
C. Observations during and after the exercise test	
Patient's effort during exercise test	Good effort
Reason(s) for stopping exercise	Why did the patient stop? Was the test stopped by the patient or the physician? Ask whether the symptoms duplicated the symptoms that ordinarily limit exercise
Data displays	Graphs and tables of data obtained during exercise test Summary tables of most important information
D. Exercise test interpretation	
Maximum exercise capacity	Absolute $\dot{V}O_2$ (mL/min), $\dot{V}O_2$ relative to size (mL/min/kg) and relative to normal subject (% predicted)
Comment on cardiovascular function, ventilation–perfusion mismatching, and breathing pattern and reserve, from the data presented in the nine-panel graphical array	Which functions are abnormal? Does $\dot{V}O_2$ increase normally as related to work rate? Is ventilatory efficiency normal? Was breathing pattern chaotic or ordered?
Link symptom when stopping to pathophysiology, and link pathophysiology to a clinical diagnosis	The $\dot{V}O_2$ abruptly stopped increasing normally when the ST segments of Std II and III and $V_4 - V_6$ of the ECG started to become depressed. Ventilatory efficiency and breathing reserve were normal. These findings are supportive of myocardial ischemia during exercise at the level of work that the patient stopped exercise because of body fatigue.

COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in 1 second; IC, inspiratory capacity; MVV, maximal voluntary ventilation; VC, vital capacity.

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CHAPTER

7

Normal Values

Interpretation of the results of exercise tests requires knowledge of the normal responses. This chapter presents values for important physiological variables that we think represent the best predictive data available for sedentary normal subjects during exercise. In some instances, several sets of normal values for the same measurement are included. When doing so, we have made recommendations as to which to use.

PREDICTED VALUES FOR ADULTS

Peak Oxygen Uptake

The selection of peak $\dot{V}_{O_2}$ predicted values (both mean and at the 95% confidence level) is a challenging problem, especially because the geographic area, body sizes, and activity levels of a specific clinical population may differ from those of reference populations. Peak $\dot{V}_{O_2}$ in normal subjects during exercise varies with age, gender, body size, lean body mass, level of ordinary activity, and type of exercise. When comparing the peak $\dot{V}_{O_2}$ of an individual to the predicted peak $\dot{V}_{O_2}$, a predicted value generated or modified for the same form of exercise should be used. It is preferable if the population from which the predicting equations were obtained included a large number of individuals with similar characteristics to the patient being tested.

Astrand and Rodahl[10] pointed out that peak $\dot{V}_{O_2}$ expressed as (mL/min) × kg^{-1} is higher in smaller compared with larger elite athletes, even when obesity is not a factor. However, when expressed as (mL/min) × $kg^{-2/3}$, peak $\dot{V}_{O_2}$ differs minimally between smaller and larger athletes. They argued against the practice of using weight as a primary variable in predicting peak $\dot{V}_{O_2}$. Despite their rational explanation and the obvious bias introduced by obesity on peak values when expressed as (mL/min) × kg^{-1}, many exercise physiologists and clinicians continue to estimate cardiovascular function by comparing actual values to values predicted from age, gender, and weight, even in obese individuals. However, this practice will predict too high a peak $\dot{V}_{O_2}$ in obese individuals. We believe that sufficient evidence now exists to assert that, even though peak $\dot{V}_{O_2}$ values may still be expressed as (mL/min) × kg^{-1} in many publications, this practice is not optimal for the clinical evaluation of the cardiorespiratory function of patients.[55,64,93]

Age and Gender

Many investigators have reported that peak $\dot{V}_{O_2}$ declines with age and is smaller for women than men.[7,41,57] Although cross-sectional studies of change in peak $\dot{V}_{O_2}$ with age are easier to perform than longitudinal studies, they may be misleading on account of selection bias.

Older subjects included in such a study are more likely to be active, relative to their peers, than their younger counterparts; hence, the peak $\dot{V}O_2$ values in older subjects in cross-sectional studies tend to decrease more slowly than peak $\dot{V}O_2$ values in longitudinal studies.[38] In a longitudinal study, Astrand et al.[8] measured $\dot{V}O_2$max during cycling exercise in 66 well-trained, physically active men and women aged 20 to 33 years and studied them again 21 years later. The mean decrease in $\dot{V}O_2$max was 22% for the 35 women and 20% for the 31 men.

Bruce et al.[22] used stepwise multiple regression analysis to identify whether gender, age, physical activity, weight, height, or smoking aided in the prediction of $\dot{V}O_2$max during treadmill exercise in adults. They found that gender and age were the two most important factors. The $\dot{V}O_2$max values of women were approximately 77% of the $\dot{V}O_2$max of men when adjusted for body weight and activity. Astrand[9] reported 17% lower $\dot{V}O_2$max for 18 women students compared with 17 male students of comparable size.

Activity Level

Investigators generally agree that values obtained from athletes, physical education teachers, servicemen, or participants in organized exercise groups are not representative as reference values for a clinical population. Balke and Ware[13] found the peak $\dot{V}O_2$ of Air Force personnel to be strongly related to their activity pattern. Drinkwater et al.[41] found that the peak $\dot{V}O_2$ of extremely active women did not decline over two decades despite a gradual increase in body weight. The decline in peak $\dot{V}O_2$ with age is more rapid in habitually inactive men, even allowing for greater weight gain in the inactive group.[38] Importantly, even brief periods of physical training can increase peak $\dot{V}O_2$ by 15% to 25% or more.[7,33]

Matching Predicting or Reference Equations to Body Size

The diagnosis of cardiovascular and other diseases depends not only on pattern analysis but also on comparing actual with predicted peak exercise values. As can be seen in Figure 7.1, the population that is referred to us for clinical exercise testing at our institution includes a great many very obese individuals. It is very likely that this situation occurs at many other locations as well. Therefore, it is essential to have predicting equations that are valid for overweight, obese, and morbidly obese patients. As illustrated in Figures 7.2 and 7.3, there are relatively small differences in predicted peak $\dot{V}O_2$ values for individuals of average height (men of 170 to 180 cm and women of 160 cm) who are not obese (body mass index [BMI] of <22 kg/m^2). However, the differences in predicted peak $\dot{V}O_2$ values become significantly more diverse when the subjects (or patients) are shorter, taller, or obese.[36,48,59,60,62,80] Because the differences are markedly exaggerated with increasing obesity, it is important and necessary to compare predicted peak $\dot{V}O_2$ values of otherwise healthy men and women at different heights, ages, and BMI levels.

Tables 7.1 and 7.2 give the constants and variables for the equations that allow one to calculate the reference or predicted values for peak $\dot{V}O_2$ in the several series displayed in Figures 7.4 and 7.5. Part of the differences between series relate to subject selection and their activity and fitness level at each site:

1. The Inbar et al.[59] equations of peak $\dot{V}O_2$ treadmill values for Israeli men have been reduced by 10% for cycle peak $\dot{V}O_2$ values. An example for men from Table 7.1 is as follows: peak $\dot{V}O_2$ in L/min = 0.9 × (−0.0227 × age in years + 0.00114 × height in cm + 0.0172 × weight in kg + 0.183). The small changes dependent on rural versus urban residence and activity level are not given nor plotted.
2. The Itoh et al.[60] equations are from leaner Japanese residents and depend on age and gender but not on weight. An example for women from Table 7.2 is as follows: peak $\dot{V}O_2$ in L/min = (−0.00023 × age in years + 0.0404) × weight in kg.

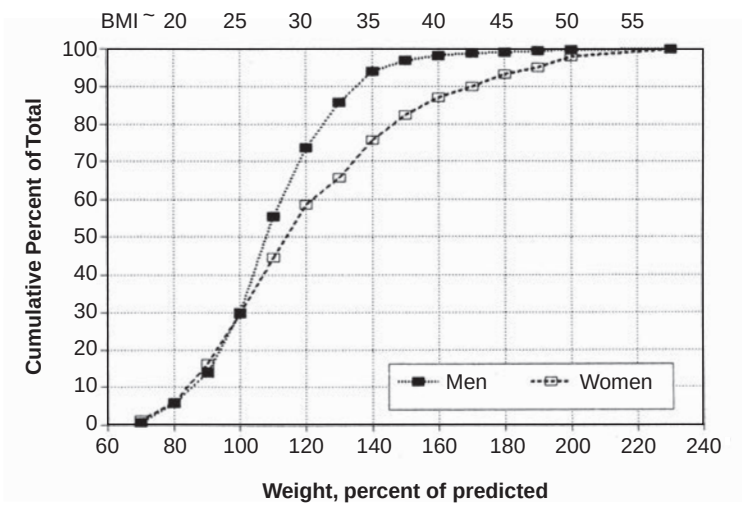

FIGURE 7.1. Cumulative percent of the total number of patients (approximately 1,000) evaluated for symptoms requiring cardiopulmonary exercise testing at Harbor-UCLA Medical Center, as related to actual body mass index (BMI; **top** *x*-axis) and percent of predicted body weight (**bottom** *x*-axis). Normal (predicted) weight for men in kilograms = 0.79 × height in centimeters – 60.7, and for women in kilograms = 0.65 × height in centimeters – 42.8. Our patient population can be seen to include a high proportion of overweight, obese, and morbidly obese individuals. (Formulas from Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J.* 1973;85:546–562.)

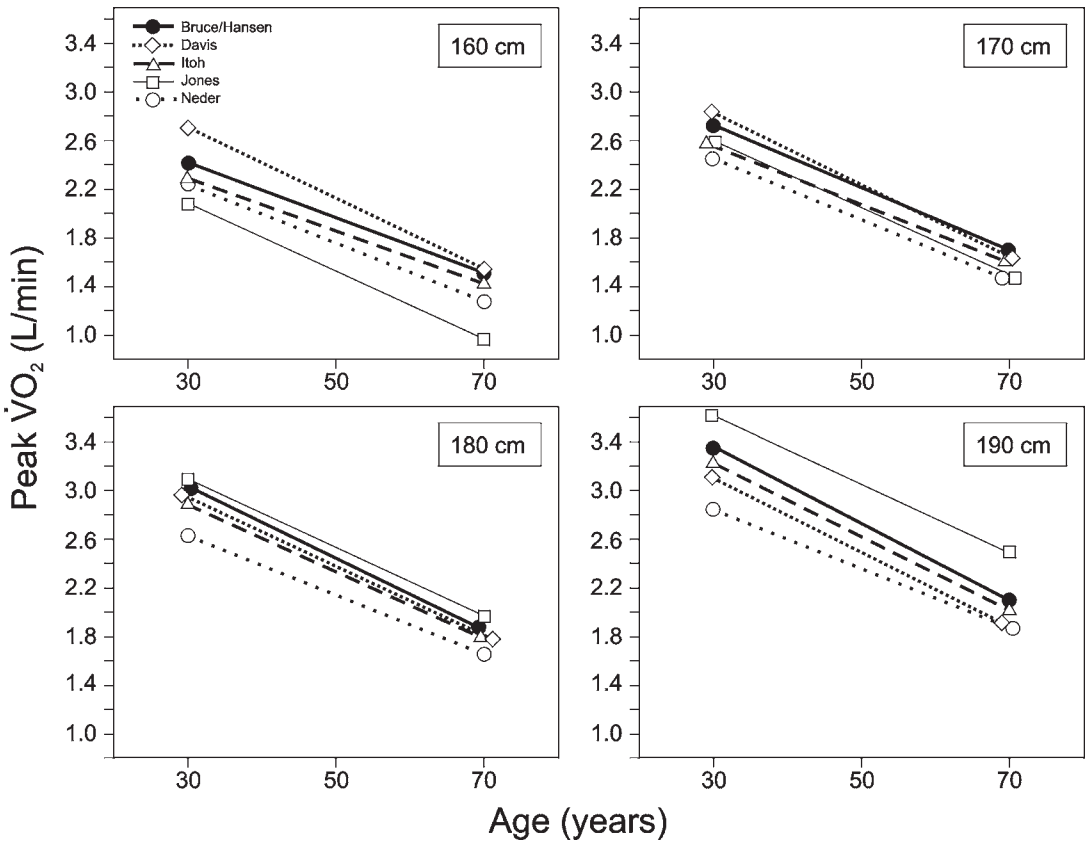

FIGURE 7.2. Comparison of predicted peak $\dot{V}O_2$ for cycle ergometry of sedentary men with body mass index of 22 calculated from five reference series for ages 30 to 70 for four different heights and weights: 160 cm and 56 kg, 170 cm and 64 kg, 180 cm and 71 kg, and 190 cm and 80 kg. (Data are from Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J.* 1973;85:546–562; Jones NL, Makrides L, Hitchcock C, et al. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis.* 1985;131:700–708; as modified by Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis.* 1984;129[pt 2]:S49–S55; Itoh H, Taniguichi K, Koike A, et al. Evaluation of severity of heart failure using ventilatory gas analysis. *Circulation.* 1990;81[suppl II]:II31–II37; Davis JA, Storer TW, Caizzo VJ, et al. Lower reference limit for maximal oxygen uptake in men and women. *Clin Physiol Funct Imaging.* 2002;22:332–338; Neder JA, Nery LE, Castello A, et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. *Eur Respir J.* 1999;14:1304–1313.)

3. Two of the three equations using Canadians that were simultaneously published by Jones et al.[62] are compared. *Jones 1* equations use height but not weight as variables; *Jones 2* equations use both height and weight.
4. The equations by Neder et al.[80] from a large population used 10 randomly selected sedentary Brazilian subjects of each gender from six decades.
5. The Study of Health In Pomerania (SHIP) equations[48] were derived from a normal large well-selected German population, including a significant portion of healthy obese subjects.
6. The Hansen/Wasserman equations from Tables 7.1 and 7.2 (compatible with Bruce/Hansen in earlier editions) are based on a large Seattle population[22] and our experience with a Southern California population of healthy asbestos-exposed men including many who were obese.[55,93] Gender, age, height, and predicted ideal weight are primary factors with secondary adjustments dependent on differences between actual and ideal weight.

Figures 7.4 and 7.5 show the variability in predicted peak $\dot{V}O_2$ between series as BMI values increase from 20 to 30 to 40. Comparing the reference values for men with BMI of 20 at all heights, the Jones 1 equations yield reference peak $\dot{V}O_2$ values well above average because they do not include weight as a variable. The Jones 2 equations, which have weight as a variable, give high reference peak $\dot{V}O_2$ values at 185 cm and 35 years, but the lowest values at 160 cm and 70 years. The Inbar and Neder reference values are slightly below average.

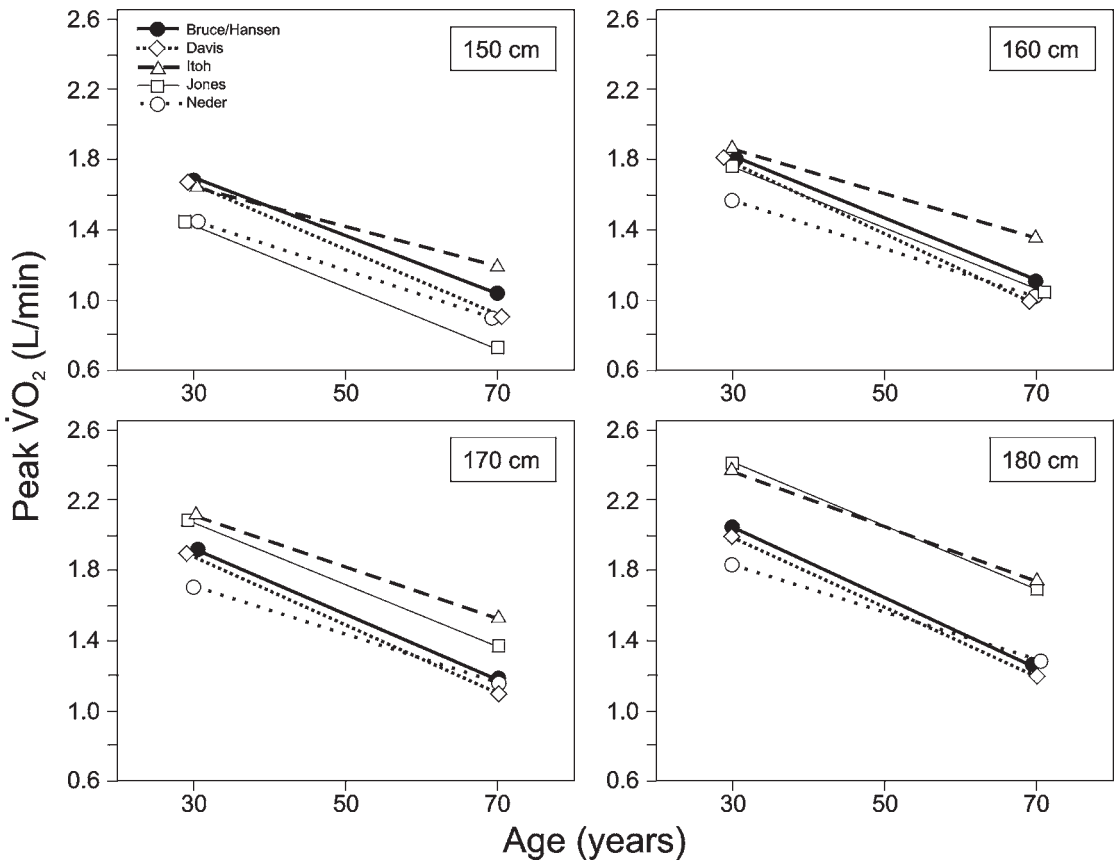

FIGURE 7.3. Comparison of predicted peak $\dot{V}O_2$ for cycle ergometry of sedentary women with body mass index of 22 calculated from five reference series for ages 30 to 70 for four different heights and weights: 150 cm and 50 kg, 160 cm and 56 kg, 170 cm and 64 kg, and 180 cm and 71 kg. (Data are from Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J.* 1973;85:546–562; Jones NL, Makrides L, Hitchcock C, et al. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis.* 1985;131:700–708; as modified by Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis.* 1984;129[pt 2]:S49–S55; Itoh H, Taniguichi K, Koike A, et al. Evaluation of severity of heart failure using ventilatory gas analysis. *Circulation.* 1990;81[suppl II]:II31–II37; Davis JA, Storer TW, Caizzo VJ, et al. Lower reference limit for maximal oxygen uptake in men and women. *Clin Physiol Funct Imaging.* 2002;22:332–338; Neder JA, Nery LE, Castello A, et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. *Eur Respir J.* 1999;14:1304–1313.)

At BMI values of 30, typical for many of our patients, Itoh's reference values are highest at 35 years, whereas the Jones 2 reference values are highest at 185 cm and lowest and 160 cm at 70 years. At BMI's of 40, Itoh and Jones 2 reference values are uniformly high. Note that the Itoh equations do not include height as a variable because the population tested was likely uniformly nonobese, typical of the Japanese people. The Hansen/Wasserman, SHIP, Neder, and Inbar equations yield relatively similar predicted values

Reference peak $\dot{V}O_2$ values for women at three differing BMI levels, are usually with more variability than for men. The Itoh and Jones 1 reference values, which do not include weight as a factor, are similar for thin, overweight, and very obese individuals, and thus vary considerably from the overall averages. At BMI of 20, Jones 1 has the highest reference values at 175 cm but very low values at 150 cm at 70 years. Itoh and Jones 2 reference values are next highest for 175 cm at 35 years and next lowest for 150 cm at 70 years. At BMIs of 30 and 40, Itoh reference values for men are lower than all others. At BMI of 30, Jones 2 reference values are high for age 70 and low for age 35 years. At BMI of 40, Jones 1 reference values are again low for 150-cm subjects regardless of age and Jones 2 reference values are high for 175-cm subjects, whereas the Neder, SHIP, and Hansen/Wasserman reference values are all reasonably similar.

Table 7.3 summarizes and quantifies the differences between reference peak $\dot{V}O_2$ values from these series. It is apparent that there are major differences in peak $\dot{V}O_2$ between the Jones 1 and 2 equations, as well as the SHIP and Hansen/Wasserman equations. Jones 1

Table 7.1

Equations for Adult Men for Prediction of Peak $\dot{V}O_2$ in L/min for Cycle

Reference	Country	Equation for peak $\dot{V}O_2$
Inbar et al.[59]	Israel	Peak $\dot{V}O_2$ = 0.9 × [0.183 + 0.0114 × Height + 0.0172 × Weight − 0.0227 × Age]
Itoh et al.[60]	Japan	Peak $\dot{V}O_2$ = 0.9 × Weight × [0.0521 − 0.00038 × Age]
Jones et al.[62] (Jones 1 equations)	Canada	Peak $\dot{V}O_2$ = −4.31 + 0.046 × Height − 0.021 × Age
Jones et al.[62] (Jones 2 equations)	Canada	Peak $\dot{V}O_2$ = −3.76 + 0.034 × Height + 0.022 × Weight − 0.028 × Age
Neder et al.[80]	Brazil	Peak $\dot{V}O_2$ = 0.702 + 0.0098 × Height + 0.0125 × Weight − 0.0246 × Age
Gläser et al.[48] (SHIP equations)	Germany	Peak $\dot{V}O_2$ = −0.069 + 0.01402 × Height + 0.00744 × Weight + 0.00148 × Age − 0.0002256 × Age × Age
Hansen et al.[52] (Hansen/Wasserman equations)	United States	Ideal weight (kg) = 0.79 × Height (cm) − 60.7 If actual weight equals or exceeds ideal weight: Peak $\dot{V}O_2$ = 0.0337 × Height − 0.000165 × Age × Height − 1.963 + 0.006 × Weight (actual − ideal) If actual weight is less than ideal weight: Peak $\dot{V}O_2$ = 0.0337 × Height − 0.000165 × Age × Height − 1.963 + 0.014 × Weight (actual − ideal) **(Use age of 30 years for adults younger than 30 years)**

Units of measure: Peak $\dot{V}O_2$, L/min; height, cm; weight, kg; age, years.

Table 7.2

Equations for Adult Women for Prediction of Peak $\dot{V}O_2$ in L/min for Cycle

Reference	Country	Equation for Peak $\dot{V}O_2$
Itoh et al.[60]	Japan	Peak $\dot{V}O_2$ = 0.9 × Weight × [0.0404 − 0.00023 × Age]
Jones et al.[62] (Jones 1 equations)	Canada	Peak $\dot{V}O_2$ = − 4.93 + 0.046 × Height − 0.021 × Age
Jones et al.[62] (Jones 2 equations)	Canada	Peak $\dot{V}O_2$ = −2.26 + 0.025 × Height + 0.01 × Weight − 0.018 × Age
Neder et al.[80]	Brazil	Peak $\dot{V}O_2$ = 0.372 + 0.0074 × Height + 0.0075 × Weight − 0.0137 × Age
Glaser et al.[48] (SHIP equations)	Germany	−0.588 + 0.00913 × Height + 0.02688 × Weight − 0.01133 × Age − 0.00012 × Weight × Weight
Hansen et al.[52] (Hansen/Wasserman equations)	United States	Ideal weight (kg) = 0.65 × Height (cm) − 42.8 Peak $\dot{V}O_2$ = 0.001 × Height × (14.783 − 0.11 × Age) + 0.006 × Weight (actual − ideal) **(Use age of 30 years for adults younger than 30 years)**

Units of measure: Peak $\dot{V}O_2$, L/min; height, cm; weight, kg; age, years.

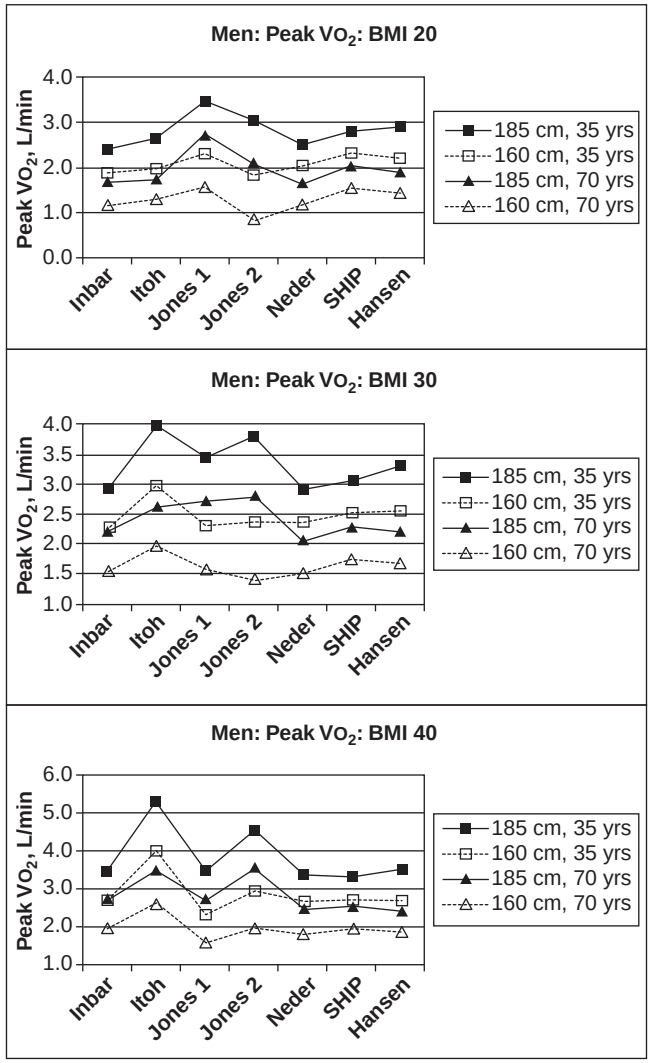

FIGURE 7.4. Comparison of predicted peak $\dot{V}O_2$ values for men of 2 ages (35 and 70 years), two heights (160 and 185 cm), and three nutritional states (body mass index of 20, 30, and 40) for seven series. (Predictive equations are from Inbar O, Oren A, Scheinowitz M, et al. Normal cardiopulmonary responses during incremental exercise in 20- to 70-yr-old men. *Med Sci Sports Exerc.* 1994;26:538–546; Itoh H, Taniguichi K, Koike A, et al. Evaluation of severity of heart failure using ventilatory gas analysis. *Circulation.* 1990;81[suppl II]:II31–II37; Jones NL, Makrides L, Hitchcock C, et al. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis.* 1985;131:700–708; Neder JA, Nery LE, Castello A, et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. *Eur Respir J.* 1999;14:1304–1313; Glaser S, Koch B, Itterman T, et al. Influence of age, sex, body size, smoking, and b-blockade on key gas exchange exercise parameters in an adult population. *Eur J Cardiovasc Prev Rehabil.* 2010;17:469–476; Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis.* 1984;129[pt 2]:S49–S55. The similarities and differences are obvious and discussed in the text.)

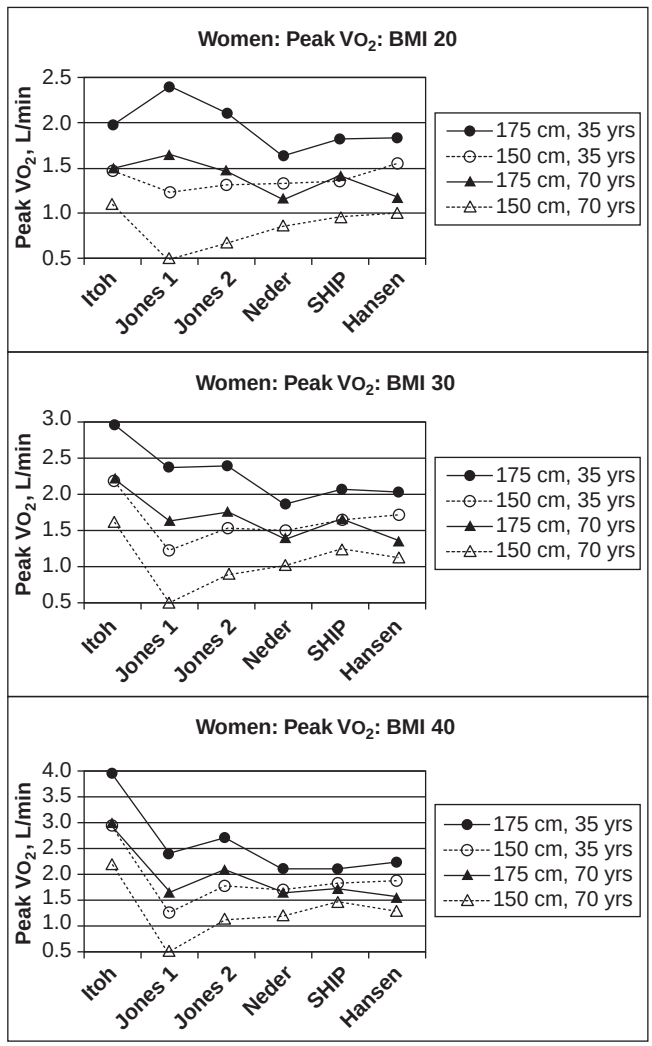

FIGURE 7.5. Comparison of predicted peak $\dot{V}O_2$ values for women of two ages (35 and 70 years), two heights (150 and 175 cm), and three nutritional states (body mass index of 20, 30, and 40) for six series. (Predictive equations are from Itoh H, Taniguichi K, Koike A, et al. Evaluation of severity of heart failure using ventilatory gas analysis. *Circulation.* 1990;81[suppl II]:II31–II37; Jones NL, Makrides L, Hitchcock C, et al. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis.* 1985;131:700–708; Neder JA, Nery LE, Castello A, et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. *Eur Respir J.* 1999;14:1304–1313; Glaser S, Koch B, Itterman T, et al. Influence of age, sex, body size, smoking, and b-blockade on key gas exchange exercise parameters in an adult population. *Eur J Cardiovasc Prev Rehabil.* 2010;17:469–476; Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis.* 1984;129[pt 2]:S49–S55. The similarities and differences are obvious and discussed in the text.)

Table 7.3

Average Absolute Differences of Peak $\dot{V}O_2$ in L/min between Several Reference Equations for Men and Women of Two Ages, Three BMIs, and Two Heights, in Order of Descending Differences

Series Compared[a]	Men	Women	Combined
Jones 1 versus Jones 2[a]	0.493	0.403	0.448
Jones 2 versus Hansen/Wasserman[b]	0.453	0.297	0.375
Jones 1 versus Hansen/Wasserman	0.307	0.437	0.372
Jones 1 versus SHIP[c]	0.307	0.400	0.353
Jones 2 versus SHIP	0.487	0.210	0.348
Inbar[d] versus SHIP	0.203	—	—
Inbar versus Hansen/Wasserman	0.187	—	—
Inbar versus Neder	0.160	—	—
Neder[e] versus SHIP	0.187	0.153	0.170
Neder versus Hansen/Wasserman	0.186	0.127	0.157
SHIP versus Hansen/Wasserman	0.110	0.127	0.119

Ages are 35 and 70 years; BMIs are 20, 30, and 40 kg/m^2; heights are 160 and 185 cm for men and 150 and 175 cm for women.
[a]Jones 1 and 2 equations are from Jones NL, Makrides L, Hitchcock C, et al. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis.* 1985;131:700–708.
[b]Hansen/Wasserman equations are from Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis.* 1984;129(pt 2):S49–S55.
[c]SHIP equations are from Glaser S, Koch B, Itterman T, et al. Influence of age, sex, body size, smoking, and b-blockade on key gas exchange exercise parameters in an adult population. *Eur J Cardiovasc Prev Rehabil.* 2010;17:469–476.
[d]Inbar equations are from Inbar O, Oren A, Scheinowitz M, et al. Normal cardiopulmonary responses during incremental exercise in 20- to 70-yr-old men. *Med Sci Sports Exerc.* 1994;26:538–546.
[e]Neder equations are from Neder JA, Nery LE, Castello A, et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. *Eur Respir J.* 1999;14:1304–1313.

and the Hansen/Wasserman reference equations were recommended by the American Thoracic Society (ATS)/American College of Chest Physicians (ACCP) committee in 2001.[3] It is also apparent that the Hansen/Wasserman and SHIP reference values are the most similar of the values considered, whereas the Neder and Inbar reference values show only small differences from the SHIP and Hansen/Wasserman reference values. Similarity does not necessarily indicate accuracy, but the large population size, careful exclusion of disease states, meticulous measurements, and well-analyzed data of the SHIP series should give some confidence that the SHIP equations and the Hansen/Wasserman, Neder, and Inbar reference values for peak $\dot{V}O_2$ are all likely to be reasonable, especially considering the diversity of values about the mean in each series.

The selection of reference equations is of importance in ascertaining whether a patient's peak $\dot{V}O_2$ and related variables (*AT* and peak O_2 pulse) are within normal limits or reduced. Over a broad age, height, and weight span, the SHIP and Hansen/Wasserman equations (Tables 7.1 and 7.2) give the most similar reference values (Table 7.3). The SHIP equations are derived from a well-selected, very large German population and differ minimally from the Hansen/Wasserman predicted values. The Inbar and Neder equations values give reference peak $\dot{V}O_2$ values, which are usually similar or only slightly lower than those of SHIP and Hansen/Wasserman equations.

Figure 7.6 shows the predicted $\dot{V}O_2$ for men and women from the Hansen/Wasserman formula, as related to actual height or predicted weight for height at given ages. These predicted $\dot{V}O_2$ values are modified if the subject is overweight or underweight, as described in the legend.

Exercise Mode

The type of exercise is an important determinant of peak $\dot{V}O_2$. Peak $\dot{V}O_2$ during arm-cranking ergometer exercise (which is inappropriate to use in evaluating most patients) is about 70% of that of leg cycling exercise[11] because of the smaller mass of muscle and lower maximum work rate achievable. Many studies[34,40,44,57,76,88,112] have shown that the peak $\dot{V}O_2$ of leg cycling is approximately 89% to 95% of the maximal values achieved with treadmill exercise. Thus, the form of ergometry and muscle groups involved must be considered when predicting peak $\dot{V}O_2$.

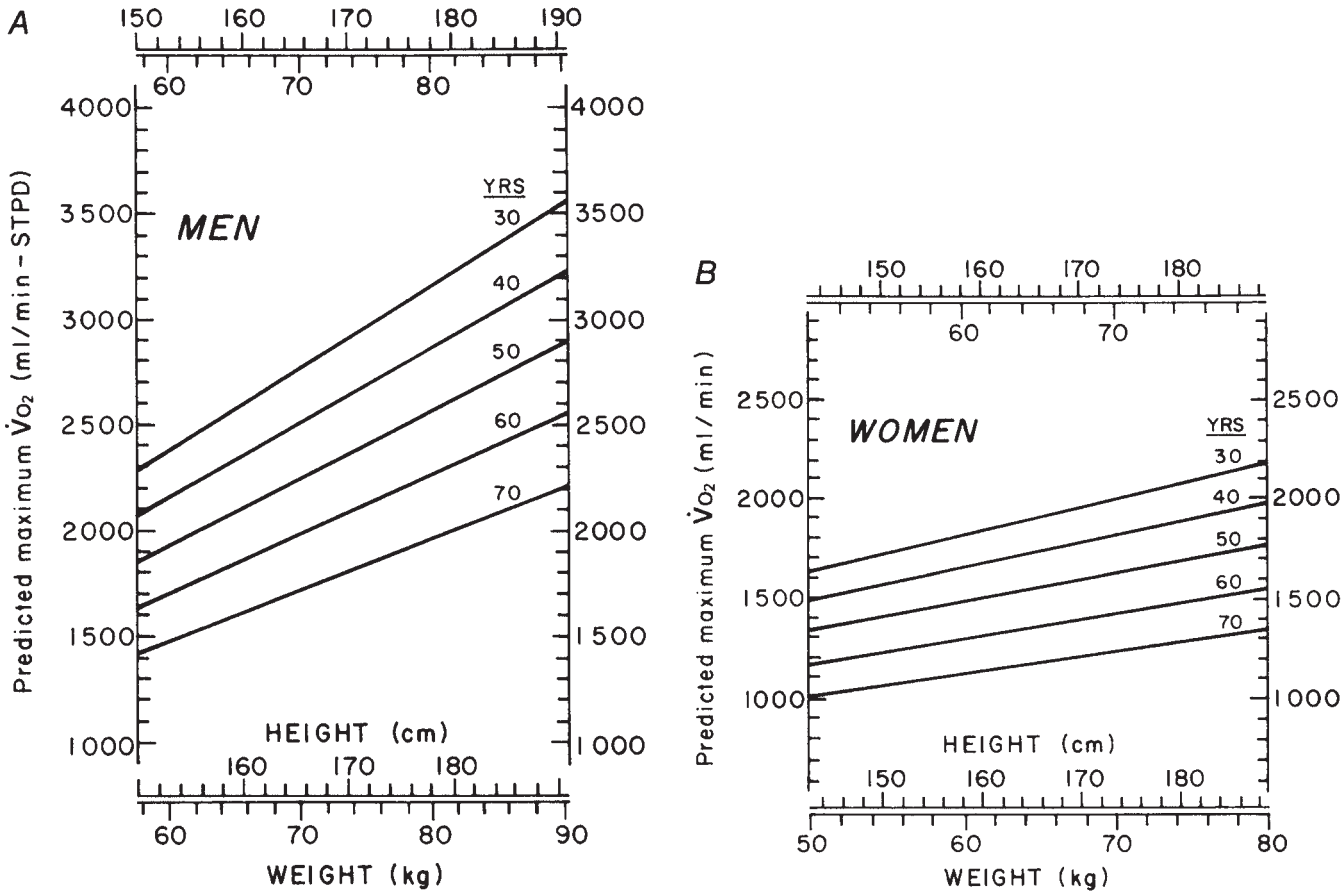

FIGURE 7.6. Mean peak $\dot{V}O_2$ values for sedentary men (**A**) and women (**B**) of normal (predicted) weight using the cycle ergometer. To use the graph to determine peak $\dot{V}O_2$, locate the patient's height and weight on the horizontal axis. If the patient (man or woman) is underweight (i.e., the patient's actual weight is to the left of that directly above the patient's height), draw a line halfway between the marks vertically to the line that indicates the patient's age. From this intersection, draw a line horizontally to the vertical axis and read off the predicted peak $\dot{V}O_2$ in liters per minute standard temperature pressure dry (STPD). If a man, the decrement in peak $\dot{V}O_2$ will be 16 mL/min for each kilogram underweight. If a woman, the decrement will be 6 mL/min for each kilogram underweight. If the patient (man or woman) is overweight (i.e., the patient's actual weight is to the right of that directly above the patient's height), draw a line vertically from the height marker to the line that indicates the patient's age. From this intersection, draw a line horizontally to the vertical axis and read off the preliminary predicted peak $\dot{V}O_2$ in liters per minute STPD. To obtain the actual predicted peak $\dot{V}O_2$ for the overweight, obese, or very obese man or woman, add 6 mL/min for each kilogram the patient is overweight. Finally, if the treadmill is used, predicted cycle values should be increased 11%. (Modified from Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J.* 1973;85:546–562. Data are from Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis.* 1984;129[pt 2]:S49–S55.)

Recommendations

- Reported peak $\dot{V}O_2$ values should preferably be based on the average of 20 or 30 seconds of data at peak exercise. It should not be based on a single breath or less than 10 seconds of data. Peak $\dot{V}O_2$ values can include data obtained one or two breaths after cessation of peak exercise, if it increases the peak value.
- Reference values for patients aged 18 to 29 years should generally be the same as for age 30 years. Therefore, for subjects of this age group, use age 30 in reference equations for peak $\dot{V}O_2$ derived for adults rather than actual age.
- The reference values given are for relatively sedentary men and women. Higher values should be expected in athletes or those who vigorously exercise during work or play. Relatively short periods (2 weeks) of extreme inactivity will reduce peak $\dot{V}O_2$ values in most individuals.
- For societies with higher levels of physical activity, the recommended predicted values may be too low. There is no good evidence that ethnicity, per se, modifies predicted values.
- For societies with very low levels of physical activity, the reference values given here may be somewhat too high.

- In sedentary populations, values of peak $\dot{V}O_2$ at 1,600 meters (1 mile) elevation above sea level will be mildly (5%) reduced; at 3,200 meters, values will be reduced by 15% to 20%.
- Medications given to relatively healthy individuals may reduce peak $\dot{V}O_2$ values. β-Adrenergic blocking drugs, especially in higher dosages, are likely to do so.
- It is wise to compare reference values from two or more series as given in Tables 7.1 and 7.2, especially for subjects at extremes of age, height, or weight. Considering the wide variability in the populations studied and the variability among reference mean values in multiple series, the lower limit of normal values should approximate 75% of the selected mean reference value.
- The SHIP or Hansen/Wasserman equations listed in Tables 7.1 and 7.2 are recommended for predicting reference values for peak $\dot{V}O_2$ in Western societies. The Inbar and Neder values are also useful in this case.

Peak Heart Rate and Heart Rate Reserve

The maximum or peak heart rate (HR) achieved declines with age in all studies. No consistent differences have been found between men and women or among the types of exercise used (e.g., leg cycling, stepping, inclined treadmill, walking, running).

The two most common formulas for predicting peak HR in adults are as follows: 220 − age (years) and 210 − 0.65 × age (years).[61] Data from this laboratory fit the former equation slightly better. The standard deviation for each formula is 10 beats per minute. As reported by Sheffield et al.[87] and Astrand and Rodahl,[10] the peak HRs derived from fit individuals approximate either formula reasonably well. The study by Cooper et al.[30] shows a lower peak HR in the less fit than the fit individual of the same age. Our finding that the peak HR was reduced in obese men is consistent with the suggestion that a sedentary existence may reduce peak HR even in well-motivated subjects.[55]

Scandinavian children were found to have an average peak HR of 205 beats per minute,[10] whereas North American children aged 8 to 18 years had an average peak HR of 187 beats per minute, with a lower 95% confidence limit of 160.[29]

The concept of heart rate reserve (HRR) can be useful for estimating the relative stress of the cardiovascular system during exercise, but it should be used with caution. A normal HRR is zero. The mean predicted peak HR may not be reached because of normal population variability, poor motivation, medications such as β-adrenergic blockers, or because of heart, peripheral vascular, lung, endocrine, or musculoskeletal diseases.

Recommendations

Peak HR values should be measured and averaged at the same time as the peak $\dot{V}O_2$ values. The following equations can be used to estimate the predicted peak HR and the HRR for adults and children:

- Maximum HR (beats/min) = 220 − age (years)
- HRR = Predicted peak HR − Observed peak HR

Relationship of Oxygen Uptake and Heart Rate: The Peak Oxygen Pulse

In a given individual, a consistent relationship exists between $\dot{V}O_2$ and HR during exercise. The quotient of the $\dot{V}O_2$ and HR is the O_2 pulse (see Figs. 4.7 and 4.8); its values are dependent on the stroke volume and the difference between the arterial and mixed venous blood O_2 content. The arteriovenous O_2 difference is, in turn, dependent on the availability of hemoglobin, arterial blood oxygenation in the lung, and net peripheral oxygen extraction.

Examples of normal and abnormal $\dot{V}O_2$ versus HR responses and O_2 pulse responses are shown in Figure 7.7. The normal relationship of $\dot{V}O_2$ with HR (patients 1 and 2) is linear over a wide range, with a positive intercept on the HR axis. Although sedentary patients 1 and 2 differ considerably in their predicted peak values (because they differ in age and gender or size), both have normal responses. An exercise response with a higher $\dot{V}O_2$/HR than predicted indicates better than average cardiorespiratory function, whereas a response with a lower $\dot{V}O_2$/HR indicates poorer than average cardiorespiratory function (patient 3). In our clinical population, this latter response is most commonly due to low stroke volume, but it could be due to anemia or carboxyhemoglobinemia, poor blood oxygenation in the lung, right-to-left shunt, or (rarely) low peripheral oxygen extraction. In patient 4, the increasing slope of the HR versus $\dot{V}O_2$ relationship for the last several minutes of exercise is abnormal, indicating that the rise in HR is disproportionately faster than $\dot{V}O_2$ as work rate increases. In patient 5, the rate of rise of the HR versus $\dot{V}O_2$ is normal, but exercise ends at a relatively low work rate. If the cessation of incremental exercise is due to pain, musculoskeletal disease, ventilatory insufficiency, or volitional, these factors (rather than circulatory disease) may be the cause of an abnormally low maximum O_2 pulse.

Differing responses can be seen in Figure 7.7A, where HR is plotted as a function of $\dot{V}O_2$ with O_2 pulse isopleths. Figure 7.7B shows O_2 pulse versus time for the same responses. Normally, the rate of increase in O_2 pulse declines gradually as the O_2 pulse approaches maximum values. This is a necessary consequence of a linear $\dot{V}O_2$ versus HR response with a positive intercept on the HR axis. This curvilinear response of the O_2 pulse during incremental exercise is clearly demonstrated in Figure 7.7B. Thus, both the peak values and the patterns of change of $\dot{V}O_2$, HR, and O_2 pulse may vary importantly in various diseases.

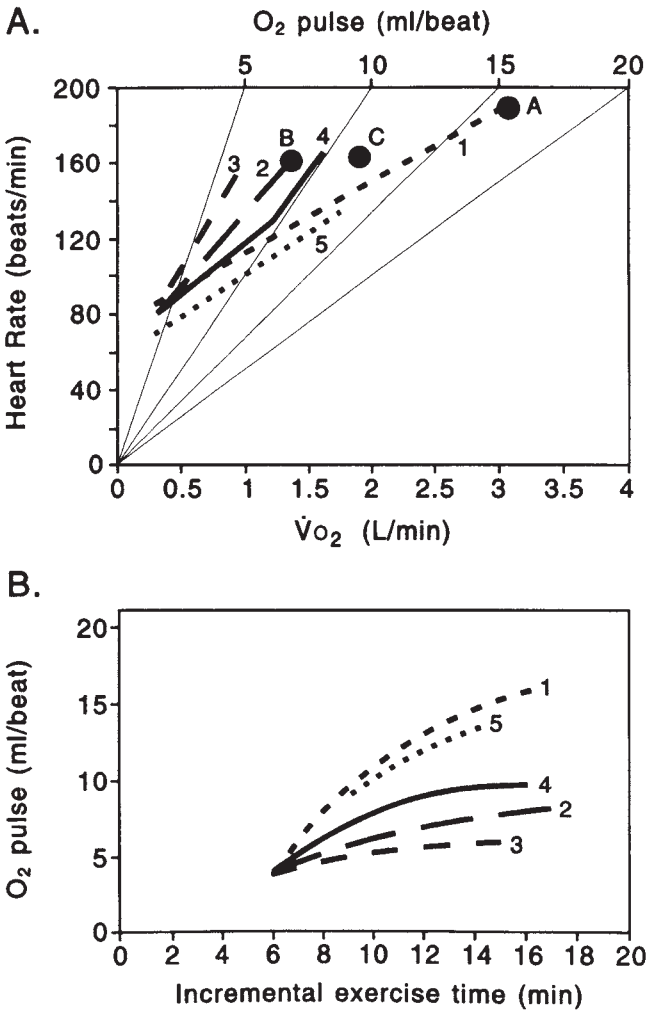

FIGURE 7.7. Values of $\dot{V}O_2$, heart rate, and O_2 pulse for five individuals during incremental cycle ergometer tests. For clarity, the resting, unloaded pedaling, and recovery data are not shown. **A:** Isopleths for O_2 pulse at 5, 10, 15, and 20 mL per beat. The three large solid circles are maximal exercise target values (each of which depends on each patient's age, gender, size, activity level, and exercise mode) and are labeled *A* for patients 1 and 5, *B* for patients 2 and 3, and *C* for patient 4. The responses for patients 1 and 2 are normal. Patient 3 had decreased cardiovascular function throughout the test and would not have reached target values even if able to exercise longer. Patient 4 manifested decreased cardiovascular function about 2 minutes before the cessation of exercise. Patient 5 stopped exercise prematurely for other than cardiovascular causes. **B**: Plots of the same O_2 pulse data against time for the five patients. Patients 1 and 2 reach their target values, whereas patients 3, 4, and 5 do not. The plateau in O_2 pulse seen for patient 4 is abnormal.

The predicted peak O_2 pulse at any given work rate is strongly dependent on the individual's body size, gender, age, degree of fitness, and hemoglobin concentration. Normal values for the predicted peak O_2 pulse on the cycle ergometer range from approximately 5 mL per beat in a 7-year-old child to 8 mL per beat in a 150-cm, 70-year-old woman, or to 17 mL per beat in a 190-cm, 30-year-old man. The actual peak O_2 pulse may be considerably higher than predicted in the cardiovascularly fit person. β-Adrenergic blocking drugs might also increase the O_2 pulse.

Recommendations

- Predicted peak O_2 pulse (mL per beat) = Predicted peak $\dot{V}O_2$ (mL per min)/Predicted peak HR (beats per min)
- Both the pattern of change as well as the absolute values of O_2 pulse should be considered.

Brachial Artery Blood Pressure

Blood pressure can be measured by auscultation during exercise by skilled technicians or physicians, but assessing the fourth Korotkoff phase diastolic pressure (muffling of sound) and the fifth Korotkoff phase diastolic pressure (disappearance of sound) may be difficult because of the background noise of the ergometer. An American Heart Association statement[2] addressed the problems related to the measurement of blood pressure by sphygmomanometry. However, intra-arterial pressures can be accurately and continuously measured by means of a pressure transducer attached to an indwelling arterial catheter whenever arterial blood specimens are not being drawn through the catheter.

The blood pressure measurements recorded in Table 7.4 are from a predominantly cigarette-smoking, sedentary normal population.[55,86] Values may be lower in nonsmoking, more active individuals. Noteworthy are the striking rise in systolic (by both cuff and direct intra-arterial recording) and mean pressures, the considerable rise in intra-arterial diastolic pressures, the modest rise in fourth-phase cuff diastolic pressures, and the gradual decline in fifth-phase cuff diastolic pressures during incremental exercise. Although resting pressures are higher in older men, the mean maximum exercise systolic and diastolic pressures are similar in both groups. Note that the true mean arterial pressure closely approximates the diastolic pressure plus half the pulse pressure, rather than one-third the pulse pressure during exercise when using a cuff.[86]

Accurate intra-arterial blood pressure values are more difficult to obtain during treadmill ergometry because of movement artifacts. When the subject is using the cycle, the hand on the handlebar stabilizes the arm and transducer, but tight gripping should be avoided to minimize the hypertensive effect of isometric exercise.

Recommendations

The brachial artery blood pressure values of nonhypertensive men, measured directly (intra-arterially) or by cuff and sphygmomanometer during 1-minute incremental exercise, are given in Table 7.4.

Table 7.4

Blood Pressure during 1-Minute Incremental Cycle Exercise Measured Directly from Catheter in Brachial Artery and in Opposite Arm by Cuff

	Prior Examination at Rest	Rest on Cycle	Exercise Near Anaerobic Threshold	Exercise Near Maximum
Sedentary, nonhypertensive men, ages 34 to 74				
Systolic intra-arterial	—	142 ± 18	182 ± 23	207 ± 27
Systolic cuff	124 ± 11	131	171	200
Diastolic intra-arterial	—	86 ± 10	92 ± 11	99 ± 12
Diastolic fourth phase	79 ± 7	84	86	88
Diastolic fifth phase	—	81	80	77
Mean intra-arterial	—	107	128	142
Sedentary, nonhypertensive men, ages 19 to 24				
Systolic intra-arterial	—	129	—	203
Diastolic intra-arterial	—	78	—	106
Mean intra-arterial	—	96	—	141

Values are mean or mean ± standard deviation in mm Hg. (Data are from Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis.* 1984;129(pt 2):S49–S55; Robinson TR, Sue DY, Huszczuk A, et al. Intra-arterial and cuff blood pressure responses during incremental cycle ergometry. *Med Sci Sports Exerc.* 1988;20:142–149.)

Anaerobic Threshold

The anaerobic threshold (*AT*) is expressed in milliliters or liters of O_2 uptake per minute. The $\dot{V}O_2$ at which the blood lactate level begins to rise has been used to define the *AT* in normal subjects[102,104] and noninvasively is best measured using the V-slope method.[16,94,103] The latter actually measures the lactic acidosis threshold, the $\dot{V}O_2$ of which is systematically a little higher than the lactate threshold for the reason described in Chapter 4. The lowest values of *AT* in a number of studies is 40% of predicted peak $\dot{V}O_2$, approximately the O_2 cost of walking at a moderate pace.[35,48,55,62] The ratio of predicted *AT* to predicted peak $\dot{V}O_2$ tends to rise with increasing age, approaching peak $\dot{V}O_2$ in the most elderly.

In nonathletes, the ratios of *AT* to predicted peak $\dot{V}O_2$ are reasonably similar for the cycle or treadmill. In athletes, the ratios of *AT* to peak $\dot{V}O_2$ are likely to be increased considerably, especially in the modes of exercise favored by the athlete.

The mode of exercise may affect the value of *AT* in normal subjects. Davis et al.[37] studied 39 healthy college-aged men. Mean $\dot{V}O_2$ at the *AT* was 46% ± 9% of peak $\dot{V}O_2$ for arm cycling, 64% ± 9% of peak $\dot{V}O_2$ for leg cycling, and 59% ± 6% of peak $\dot{V}O_2$ for treadmill exercise. A substantial difference was noted between the *AT* during arm cycling and either form of leg exercise, but no significant difference existed between the *AT* obtained from cycle exercise and that obtained from treadmill exercise. Buchfuhrer et al.[23] found similar ratios of *AT* to peak $\dot{V}O_2$ for treadmill and for cycle exercise: 50% ± 9% and 47% ± 11%, respectively. Withers et al.,[111] however, comparing highly trained cyclists and runners, found a higher *AT* for the total group on the treadmill (mean 76% of peak $\dot{V}O_2$) than on the cycle (mean 64% of peak $\dot{V}O_2$), with the cyclists reaching higher *AT* and *AT*/peak $\dot{V}O_2$ on the cycle and runners reaching higher *AT* and *AT*/peak $\dot{V}O_2$ on the treadmill.

Recommendations

Reference values for mean and lower limit of normal *AT* values for sedentary nonathletes, as related to reference values for peak $\dot{V}O_2$, are given in the text and Table 7.5.

Oxygen Uptake–Work Rate Relationship

When a progressively increasing work rate test is initiated, a delay occurs before oxygen uptake begins to increase in a linear fashion. This delay must be considered in the calculation of the overall value of the oxygen uptake–work rate relationship ($\Delta\dot{V}O_2/\Delta WR$). This kinetic delay is equal to the time constant of $\dot{V}O_2$ following a stepwise increase, is accounted for by the kinetics of muscle O_2 utilization, and is normally between one-half

Table 7.5

Mean and Lower 95% Confidence Limits for Ratio of Predicted Anaerobic Threshold to Predicted Peak $\dot{V}O_2$ in Adults, as a Percentage

	Men		Women	
Age (year)	Mean	Lower 95% Limit	Mean	Lower 95% Limit
25	50	40	53	40
35	52	42	55	42
45	54	44	57	44
55	56	46	59	46
65	58	48	61	48
75	60	50	63	50

(Data are from Jones NL, Makrides L, Hitchcock C, et al. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis.* 1985;131:700–708; Davis JA, Storer TW, Caiozzo VJ. Prediction of normal values for lactate threshold estimated by gas exchange in men and women. *J Appl Cardiol.* 1997;76:157–164; Glaser S, Koch B, Itterman T, et al. Influence of age, sex, body size, smoking, and b-blockade on key gas exchange exercise parameters in an adult population. *Eur J Cardiovasc Prev Rehabil.* 2010;17:469–476; Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis.* 1984;129 [pt 2]:S49–S55.)

and three-quarters of a minute. Thus, the formula used to calculate $\Delta\dot{V}O_2/\Delta WR$ is:

$$\Delta\dot{V}O_2/\Delta WR = (\text{Peak } \dot{V}O_2 - \text{Unloaded } \dot{V}O_2)/[(T - 0.75) \times S]$$

where $\dot{V}O_2$ is measured in milliliters per minute, T is the time of incremental exercise, and S is the slope of work rate increment in watts per minute.[54] The $\Delta\dot{V}O_2/\Delta WR$ relationship can be calculated by linear regression during the entire incremental exercise test or during specific portions of the test.

The overall $\Delta\dot{V}O_2/\Delta WR$ during incremental cycle ergometer exercise varies modestly with the slope of work rate increase, the cardiovascular fitness of the individual, and the duration of the test.[53,54] In 10 normal young men, tests of approximately 15 minutes' duration (15-W/min increment) gave higher $\Delta\dot{V}O_2/\Delta WR$ values (11.2 ± 0.15 mL/min/W) than tests of approximately 5 minutes' duration (60-W/min increment) (8.8 ± 0.15 mL/min/W). The change in $\Delta\dot{V}O_2/\Delta WR$ occurred primarily above the *AT*. $\Delta\dot{V}O_2/\Delta WR$ below the *AT* was not significantly affected by the rate of work rate increase. In tests of long duration (slowly increasing work rate tests), a higher fraction of the total energy cost of the work above the *AT* is supported by oxygen transport relative to anaerobic sources (e.g., lactate production). In contrast, a lower fraction of the total energy cost of work is derived from oxygen extracted from the inspired air, above the *AT* in the rapidly increasing work rate test. Thus, $\Delta\dot{V}O_2/\Delta WR$ is slightly greater for the slower increasing work rate test (Fig. 2.27).

The reverse allocation of energy support occurs in maximal tests of short duration. In tests of intermediate duration, however, the mean ± the standard error of $\Delta\dot{V}O_2/\Delta WR$ found in 10 normal young men[53] was 10.2 ± 0.16 mL/min/W, and in 54 older sedentary normal men[54] the mean ± the standard deviation (SD) was 10.3 ± 1.0 mL/min/W. The mean ± SD of 17 normal men was 9.9 ± 0.7 mL/min/W (Fig. 4.2). Jones et al.[62] also found a $\Delta\dot{V}O_2/\Delta WR$ of 10.3 mL/min/W in 100 healthy adult men and women. This range is small enough that the $\Delta\dot{V}O_2/\Delta WR$ is clinically useful in identifying patients with circulatory disorders.

Most patients with circulatory disorders have a significantly reduced $\Delta\dot{V}O_2/\Delta WR$,[12,53,54,89] notably above their *AT*. The most obvious reason is that O_2 transport is inadequate to perform the work. Thus, anaerobic metabolism (anaerobic glycolysis with lactate as the byproduct) contributes a larger proportion of the total energy requirement than normal.

We have seen that athletes may have a higher than average $\Delta\dot{V}O_2/\Delta WR$ (in the range of 11 to 12 mL/min/W) when cycling, perhaps due to their tendency to involve arm, chest, abdominal, and back musculature more than nonathletes.

Recommendations

For incremental cycle ergometry exercise of 6 to 12 minutes' duration, the $\Delta\dot{V}O_2/\Delta WR$ for sedentary adults is 10.0 mL/min/W, with a standard deviation of 1.0 mL/min/W and a lower limit of normal at the 95% confidence level of 8.4 mL/min/W.

Ventilatory Limitation during Exercise

Exercise Ventilation and Breathing Reserve

Maximum exercise minute ventilation ($\dot{V}E$) is similar for leg cycling, treadmill walking, and running,[23,57] but is less for arm cycling[37] because the maximal metabolic rate is lower when smaller muscle groups are used. The breathing reserve relates the ventilatory response during maximum exercise to the maximum ability to breathe. Because normal, untrained subjects do not ordinarily have ventilatory limitations in their ability to perform work,[3] some ability to increase ventilation further is usually present during maximal exercise. This potential increase in ventilation is generally estimated from the maximal voluntary ventilation (MVV), a test performed at rest. The MVV is highly dependent on the subject's motivation and effort. Normal values for MVV tests lasting 12 and 15 seconds are available.[66,72] The difference between the measured MVV and the maximum $\dot{V}E$ during exercise is used as a measure

of the ventilatory or breathing reserve. A low breathing reserve suggests that a subject's exercise capacity may be limited by his or her ventilatory capacity. The breathing reserve is usually reduced in patients with moderate to severe restrictive or obstructive lung disease (see Fig. 5.9).

Many investigators have examined the normal relationship between the MVV and the maximum exercise $\dot{V}E$. Maximum exercise $\dot{V}E$ averages 50% to 80% of the 12- or 15-second MVV, indicating a breathing reserve of 20% to 50% of the MVV. Because the MVV is dependent on the subject's cooperation, effort, and technique of performance, the MVV is sometimes indirectly estimated from the FEV_1 or $FEV_{0.75}$. Gandevia and Hugh-Jones[46] suggested that the indirect MVV could be estimated as $FEV_1 \times 35$, whereas Cotes[31] suggested $FEV_{0.75} \times 40$ or $(36.8 \times FEV_1 - 2.8)$. Miller and colleagues[78] found that $FEV_1 \times 41$ or $FEV_{0.75} \times 46$ best estimated MVV.

Our data[55] and those of Campbell[24] indicate that $FEV_1 \times 40$ provides an optimal estimate of the direct MVV both in normal subjects and in patients with obstructive lung disease. If the directly measured MVV is less than the indirectly measured MVV ($FEV_1 \times 40$), poor cooperation or understanding in the performance of the maneuver, extreme obesity, neurologic disorders, or inspiratory obstruction may be possible causes. If one is uncertain regarding a discrepancy between the direct MVV and the indirect MVV, or if the patient has variable obstruction, it may be necessary to have the patient repeat the direct MVV measurement or to accept the $FEV_1 \times 40$, which should be a more reproducible measurement. In the case of patients with interstitial lung disease, it is common for them to have direct MVV values, which are 50 or 60 times the FEV_1. This is likely due to the fact that they have strong ventilatory muscles, have increased elastic recoil so that their airways do not tend to collapse during forced exhalations, and their breathing frequencies during the MVV tests are very high, sometimes as high as 100 to 120 breaths per minute. Because such high breathing frequencies are not achieved during cardiopulmonary exercise testing (CPET) and their direct MVV values can markedly exceed $FEV_1 \times 40$, we now recommend that the indirect MVV ($FEV_1 \times 40$) be used in calculating breathing reserve.

In 77 normal middle-aged subjects participating in an incremental cycle ergometer exercise test clinical study,[55,93] the mean direct MVV was 131 ± 23.6 L per min (range 81–203 L/min). The mean maximum exercise $\dot{V}E$/MVV was 71.5% ± 14.6%; only 13 subjects had a value greater than 80%. When we used $FEV_1 \times 40$ as an indirect estimate of the MVV, the mean maximum exercise $\dot{V}E$/indirect MVV was 71.5% ± 15.3%, the same percentage as for the directly measured MVV. By expressing breathing reserve as MVV minus maximum exercise $\dot{V}E$, we obtained an average of 38.1 ± 22.0 L per min using the directly measured MVV and 38.0 ± 21.5 L/min using the indirect MVV. We consider it likely that the patient is ventilatory limited when the breathing reserve is less than 11 L/min.

Tidal Volume and Breathing Frequency

We consider that patients have ventilatory limitation if the exercise tidal volume (VT) reaches the resting inspiratory capacity (IC), particularly early during a progressively increasing work rate test, or if the breathing frequency (f) exceeds 50 breaths per minute (bpm). The expected maximum exercise VT, like ventilatory capacity and other resting pulmonary function measurements, depends on the subject's height, age, and gender. In addition, the dead space or rebreathed volume of the breathing apparatus influences ventilation.[19,63,70]

Hey et al.[58] recommended that VT be related to $\dot{V}E$ to analyze the breathing pattern, such as is shown in Figure 4.13. At low exercise intensity, the increase in $\dot{V}E$ is accomplished primarily by an increase in VT. After the VT reaches approximately 50% to 60% of the VC, further increases in $\dot{V}E$ are accomplished primarily by increasing f.[31,90] Thus, f is a curvilinear function of $\dot{V}E$. Spiro et al.[90] found that the maximum VT reached by normal subjects was approximately 55% of VC in normal men and 45% in normal women. In contrast, Cotes[31] suggested that maximum VT is about 50% of VC for VC values between 2.0 and 5.0 L in normal men and women of European descent. Astrand and Rodahl[10] found that, at maximal exercise, the VT averaged between 1.9 and 2.0 L, or 52% to 58% of the VC, whereas f at maximal exercise ranged between 34 and 46 bpm. Little difference in VT/VC was noted among age groups, but f was lower in the older subjects studied.

Wasserman and Whipp[106] compared exercise VT to IC. They found that VT does not usually exceed approximately 70% of the IC during exercise, but it increases to a value approaching 100% in patients with restrictive lung disease, suggesting that the IC may limit the increase in VT (see Fig. 4.13). In a series of 77 healthy middle-aged men, the mean resting VT of 0.71 ± 0.26 L increased to 1.44 ± 0.43 L at the *AT* and 2.28 ± 0.43 L at maximum exercise.[55,93] Maximum f was 41.6 ± 9.6 min^{-1}. Maximum VT averaged 70.0% ± 10.7% of the IC and 55.0% ± 8.7% of the VC. No one had a maximum exercise VT greater than his resting IC, and only three had a maximal exercise f greater than 60 min^{-1}.

Partitioning the duration of the ventilatory cycle duration (TTOT) into inspiratory (TI) and expiratory (TE) times may also prove useful. However, this measurement is not commonplace in clinical exercise testing. TI/TTOT should increase during exercise due to shortening of TE.

End-tidal CO_2

Ordinarily, the $PETCO_2$ values increase several mm Hg from resting levels during moderate exercise, peaking be-

tween the *AT* and ventilatory compensation point (VCP), then decreasing toward peak exercise in response to the ventilatory compensation for the developing lactic acidosis. Patients who are severely ventilatory limited may be unable to increase their ventilation appropriately in response to the acidemia and, therefore, have a stable or rising alveolar, arterial, and end-tidal CO_2 pressure above the *AT*.

Recommendations

- Use indirect MVV ($FEV_1 \times 40$) rather than direct MVV unless there are compelling circumstances (e.g., inspiratory obstruction or severe neuromuscular disorder) to do otherwise.
- Use the direct MVV to test for respiratory muscle fatigue or weakness (e.g., myasthenia gravis).
- Breathing reserve = MVV − highest $\dot{V}E$ during exercise averaged during a 20- to 30-second period.
- Breathing reserve <10% of indirect MVV or <11 L/min is likely abnormal, indicating ventilatory limitation to exercise.
- *f* uncommonly exceeds 55/min except in athletes and interstitial lung disease.
- Exercise VT uncommonly reach more than 85% to 90% of resting IC volumes. Higher percentages often occur with interstitial lung disease.
- Rising end-tidal values of CO_2 at end of exercise likely indicate ventilatory limitation to exercise.

Gas Exchange Relationships: $\dot{V}E$ to $\dot{V}CO_2$ and $\dot{V}O_2$

Because ventilation is more closely linked to CO_2 output than O_2 uptake, ventilatory efficiency is best defined by the relationship of the liters of ventilation required to eliminate a liter of CO_2. Mathematically, this relationship can be expressed either as a ratio or a slope (see Fig. 4.21), with the only factors being dead space/tidal volume ratio (VD/VT), $PaCO_2$, $\dot{V}E/\dot{V}CO_2$, and a constant to adjust for pressures standard temperature pressure dry (STPD) and body temperature pressure saturated (BTPS) and to convert fractional concentrations to pressures:

$$\dot{V}E/\dot{V}CO_2 = k/[PaCO_2 \times (1 - VD/VT)]$$

Practically, the efficiency or inefficiency of elimination of CO_2 is measured as $\dot{V}E/\dot{V}CO_2$ at the level of ventilation that is least variable between the *AT* and the VCP. It can be affected by $PaCO_2$ and VD/VT as shown in the preceding equation. $PaCO_2$ is particularly dependent on factors affecting H^+ regulation, as shown in Chapter 2, with transient changes due to acute hyper- or hypoventilation. VD/VT is particularly affected by ventilation-perfusion mismatching and the size of the anatomical deadspace. Thus, $\dot{V}E/\dot{V}CO_2$ is a quotient that describes the ventilation needed to eliminate 1 L of metabolic CO_2 at the level of ventilation that is least variable between the *AT* and the VCP. Because these parameters are strongly affected by the presence, absence, or changes in lung gas exchange caused by both lung and heart diseases, the measurement of $\dot{V}E/\dot{V}CO_2$ at the *AT* or VCP (measurements which are similar) are clinically very useful.

The relationships between $\dot{V}E$ and $\dot{V}CO_2$ and between $\dot{V}E$ and $\dot{V}O_2$ are important.[107] $\dot{V}E/\dot{V}CO_2$, measured between the *AT* and VCP, is most reproducible and a measure of ventilatory efficiency for the clearance of CO_2 from the body—that is, the liters of $\dot{V}E$ (BTPS) required to eliminate 1 L of CO_2 (STPD).[96] The higher the value, the more inefficient is ventilation in achieving gas exchange with the pulmonary blood flow. As described in Chapters 2 and 4, the increase in $\dot{V}E/\dot{V}O_2$ from its low nadir, while $\dot{V}E/\dot{V}CO_2$ remains constant at a low value or continues to decrease, indicates stimulation of ventilation disproportionate to $\dot{V}O_2$. This disproportionate $\dot{V}E$ stimulus has been shown to be H^+ accompanying the lactic acidosis of the *AT*.[107]

The slope of $\dot{V}E$ (BTPS) versus $\dot{V}CO_2$ (STPD) has been characterized in patients[25,47,65,77,108] and normal subjects[31,59,65,80,48,96,105] to evaluate their relationship. We compared the variability between several large series of normal subjects that measured slopes only below the ventilatory compensation point to assess similarities and dissimilarities. For women, we compared the formulas of Kleber et al.[65], Neder et al.[80], the SHIP investigators[48], and Sun et al.[96] at ages 30 and 70 years with normal heights and BMIs. We added the formula of Inbar et al.[59] for men. The formulas of Sun et al., Neder et al., and Kleber et al. showed the least variability from the overall means, with absolute differences of 0.8, 1.0, and 1.6 units, respectively. Their formulas for $\dot{V}E$ versus $\dot{V}CO_2$ slope are:

Sun et al.[96] = 34.4 − 0.0723 cm + 0.082 years (SD 3.0) for both genders
Neder et al.[80] = 21.0 + 0.12 years (SD 2.5) for men
= 25.2 + 0.08 years (SD 2.8) for women
Kleber et al.[65] = 19.9 + 0.13 years (SD 4.0) for men
= 24.4 + 0.12 years (SD 4.0) for women

The differences between these series in $\dot{V}E$ versus $\dot{V}CO_2$ slopes were small.

To evaluate ventilatory efficiency or inefficiency for gas exchange at the lungs, Sun et al.[96] measured $\dot{V}E/\dot{V}CO_2$ ratios at the *AT* and at their lowest level. They are virtually identical (see applicable cases in Chapter 10) and have less variability than the slope calculation, which normally has an intercept on the $\dot{V}E$ axis. The slope variability might be primarily due to various states of hyperventilation and varying dead space ventilation with changing tidal volumes, To evaluate ventilatory inefficiency in patients or

Table 7.6

Ventilatory Efficiency during Exercise for Men[a]

Age (years)	*n*	$\dot{V}e$ vs $\dot{V}CO_2$ Slope	Lowest $\dot{V}e/\dot{V}CO_2$
<20	46	22.9 ± 2.8	23.5 ± 2.0
21–30	90	23.6 ± 2.8	23.9 ± 2.1
31–40	49	23.9 ± 3.1	25.0 ± 2.7
41–50	37	25.2 ± 2.9	26.1 ± 2.2
51–60	54	27.2 ± 3.0	28.0 ± 2.9
>60	34	27.5 ± 3.1	29.4 ± 2.3

[a]To determine values for women, add 1 to the values shown for men.
(From Sun XG, Hansen JE, Garatachea N, et al. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med*. 2002;166:1443–1448, with permission.)

athletes, we recommend lowest $\dot{V}E/\dot{V}CO_2$ ratios or the $\dot{V}E/\dot{V}CO_2$ at the *AT*, described by Sun et al.[96] (see Table 7.6):

$$\dot{V}E/\dot{V}CO_2 \text{ at } AT = 28.2 + 0.105 \text{ years} - 0.0375 \text{ cm} + 1.0 \text{ for women (SD 2.39)}$$
$$\dot{V}E/\dot{V}CO_2 \text{ at lowest level} = 27.9 + 0.106 \text{ years} - 0.0376 \text{ cm} + 1.0 \text{ for women (SD 2.43)}$$

The advantages to the lowest $\dot{V}E/\dot{V}CO_2$ formula of Sun et al.[96] are the following:

1. The standard deviation around the mean is least.
2. There is the least difference between the lowest $\dot{V}E/\dot{V}CO_2$ values and the $\dot{V}E$ versus $\dot{V}CO_2$ slope values.
3. It is not necessary to identify the *AT* to use the lowest $\dot{V}E/\dot{V}CO_2$ ratios.

Recommendations

- $\dot{V}CO_2$ (STPD), $\dot{V}O_2$ (STPD), and $\dot{V}E$ (BTPS) should be measured and calculated synchronously over the same period(s) of time.
- In all calculations, mouthpiece mechanical dead space ventilation (usually approximating 50 to 60 mL per breath) should be subtracted from overall $\dot{V}E$.
- $\dot{V}E$ versus $\dot{V}CO_2$ slope should be calculated from rest or onset of exercise to ventilatory compensation point by linear regression for men or women. $\dot{V}E/\dot{V}CO_2$ = 34.4 − 0.0723 cm + 0.082 years (For both genders, SD = 3.0 and upper limit of normal (ULN) = mean predicted + 4.9).
- Lowest $\dot{V}E/\dot{V}CO_2$ or $\dot{V}E/\dot{V}CO_2$ at *AT* for men = 27.9 + 0.106 years − 0.0376 cm. Add 1.0 for women. (For both genders, SD = 2.43 and ULN = mean predicted + 4.0).

Physiological Dead Space–Tidal Volume Ratio

The physiological dead space (VD) is dependent on anatomic and physiological factors, whereas the physiological dead space–tidal volume ratio (VD/VT) is also dependent on the pattern of breathing. At rest, the VD/VT may be elevated because of rapid shallow breathing or anxiety. Physiological control mechanisms usually stabilize VD/VT at a lower, more efficient breathing pattern soon after the onset of exercise (Fig. 7.8) in normal subjects. Calculation of the VD and VD/VT must be carefully performed, making an adjustment for the apparatus dead space (see Appendix C). In addition, gas exchange measurements must be synchronous with arterial blood sampling for measuring $PaCO_2$.

All studies have shown a fall in VD/VT during exercise in normal subjects. Thus, although mean VD/VT at rest ranged from 0.28 to 0.35 in several studies of normal subjects, mean VD/VT decreases to approximately 0.20 soon after exercise starts (Fig. 7.8). It remains at about this level to the end of exercise, regardless of the level of work.[55,63,105,110]

Figure 7.8 shows the effect of exercise on VD/VT at various levels of cycle exercise in normal young men. As can be seen, the VD/VT stabilizes at a new low value soon after exercise starts and is slightly lower at higher work rates. Cotes[31] suggested that VD (mL) equals 140 + 0.07 VT (mL) with an SD of 90 mL in young men during exercise. Jones et al.[63] found the following relationship during exercise in 17 normal young men: VD (mL) = 138 + 0.077 VT (mL), with $r = 0.69$. Lifshay et al.[70] showed that men aged 50 to 81 had a significantly higher VD than men and women aged 18 to 37 years. The prediction equations of Bradley et al.[18] for VD use sex, age, height, $\dot{V}CO_2$, $\dot{V}E$, *f*, and temperature as factors.

The practice of some manufacturers of offering a calculation of "noninvasive VD/VT" is invalid. This calculation substitutes $PETCO_2$ for $PaCO_2$ in the alveolar mass balance equation rearranged to allow VD/VT calculations. Use of $PETCO_2$ in place of $PaCO_2$ tends to normalize the VD/VT measurement.

Recommendations

Normal values for VD/VT at rest and during upright exercise after allowance for valve dead space are as follows:

- *For men under age 40:*
  VD/VT (mean ± SD) = 0.29 ± 0.06 at rest
  = 0.17 ± 0.05 at the *AT*
  = 0.16 ± 0.04 at maximum exercise
- *For men over age 40:*
  VD/VT (mean ± SD) = 0.30 ± 0.08 at rest
  = 0.20 ± 0.07 at the *AT*
  = 0.19 ± 0.07 at maximum exercise[55]

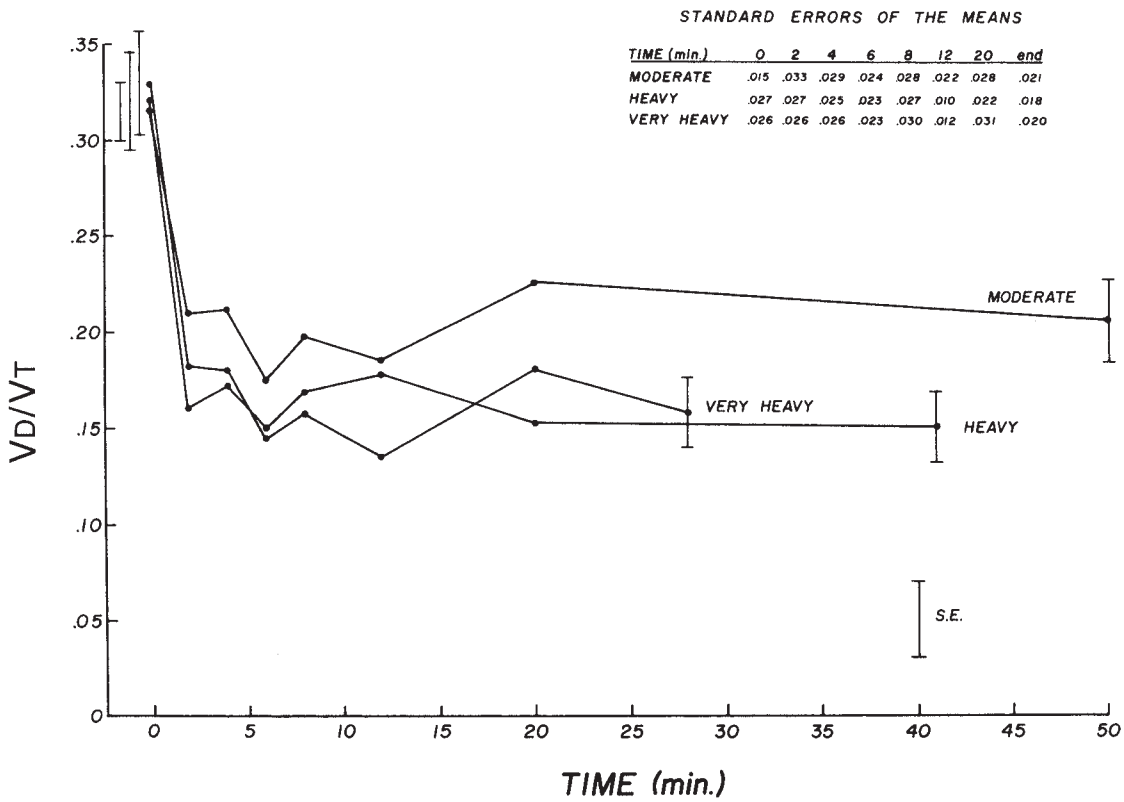

FIGURE 7.8. The physiological dead space–tidal volume ratio (VD/VT) in 10 normal young men at rest and during three intensities of cycle ergometer exercise as related to exercise time. The standard errors of the means (SEM) are given in the table inset. (From Wasserman K, VanKessel A, Burton GB. Interaction of physiological mechanisms during exercise. *J Appl Physiol.* 1967;22:71–85, with permission.)

- *Upper 95% confidence limits for men over 40:*
  VD/VT = 0.45 at rest
  = 0.33 at the *AT*
  = 0.30 at maximum exercise[55]
- $P_{ET}CO_2$ values or other values calculated from $P_{ET}CO_2$ should not be used to calculate VD/VT, despite the fact that many manufacturers of exercise and metabolic equipment continue to do so. VD/VT can only be calculated from arterial or arterialized blood. Free flowing microvascular blood from the ear lobe or finger is likely to have P_{CO_2} values that are reasonably similar to direct arterial P_{CO_2} values and result in reasonable estimates of VD/VT.

Arterial, End-Tidal, and Mixed-Expired Carbon Dioxide Pressures

Resting $P_{ET}CO_2$ and Pa_{CO_2} values are dependent on the degree of apprehension, anxiety, and training of the subject. Many anxious individuals have a strong tendency to hyperventilate, especially while breathing through a mouthpiece and awaiting the signal to begin exercise (Fig. 7.9). Once exercise starts, however, the blood gases and pH are not discernibly different whether the individual is performing the work while breathing through a low resistance breathing valve or breathing normally without a mouthpiece.[106] In more apprehensive individuals, the Pa_{CO_2} values rise from rest to moderate exercise as physiological control mechanisms suppress psychogenic hyperventilation. In the relaxed individual, Pa_{CO_2} values remain relatively stable at rest and during mild and moderate exercise. Although Pa_{CO_2} values cannot be predicted accurately from $P_{ET}CO_2$ values in an individual, particularly in a patient with lung disease, measurement of $P_{ET}CO_2$ is often valuable for following trends in Pa_{CO_2}.

Wasserman et al.[106] found that $P(a - ET)CO_2$ changed from approximately +2.5 mm Hg at rest to −4 mm Hg during heavy work in 10 normal men (Fig. 7.10). Jones et al.[63] found that in 17 normal subjects at the highest work rates reached, $P_{ET}CO_2$ was always more than 2 mm Hg higher than Pa_{CO_2}. In five normal men, Whipp and Wasserman[110] found that $P(a - ET)CO_2$ was 2.8 ± 1.6 mm Hg at rest and −2.8 ± 0.6 mm Hg at a work rate of 220 W. All $P(a - ET)CO_2$ values were negative for work rates above 115 W. In 77 asbestos-exposed healthy men,[55,93] $P(a - ET)CO_2$ at rest was 0.3 ± 2.9 mm Hg (mean ± SD) and decreased to −4.1 ± 3.2 mm Hg at maximum exercise.[55] At the peak

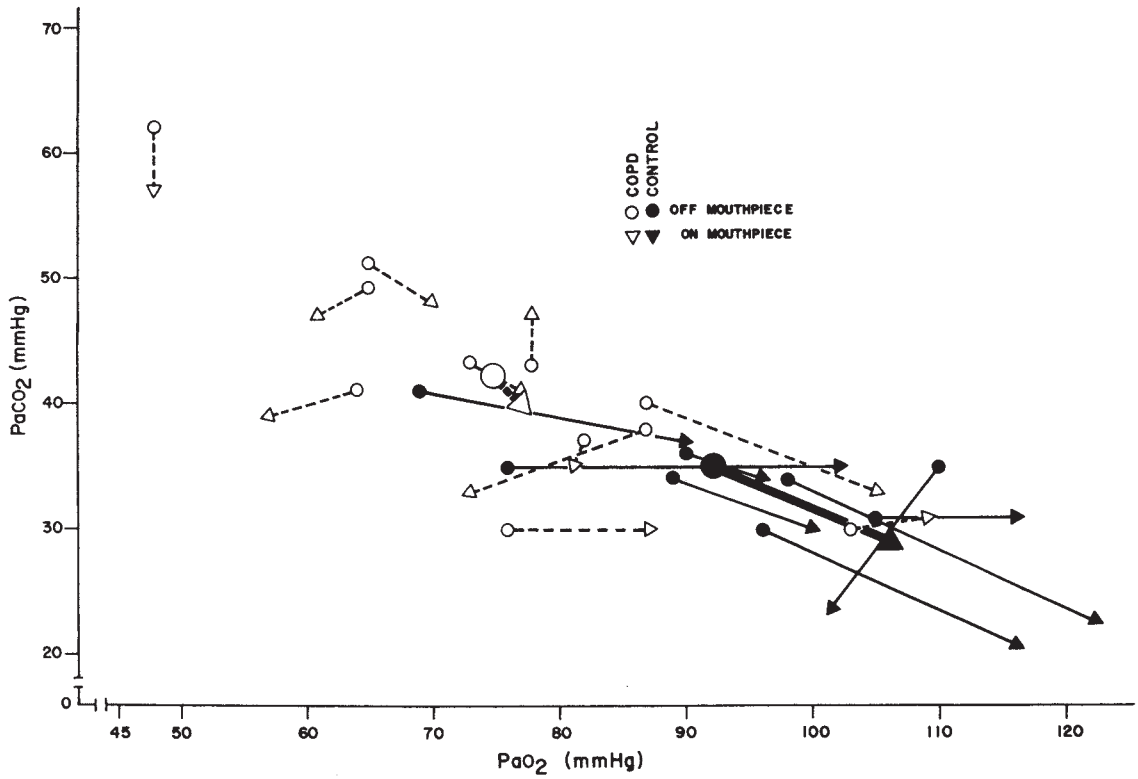

FIGURE 7.9. Resting arterial partial pressures of CO_2 ($Paco_2$) and O_2 (Pao_2) in normal control subjects and in patients with chronic obstructive pulmonary disease (COPD) off and acutely on the mouthpiece while awaiting the signal to start cycle ergometer exercise. Small arrows show individual values, and large arrows show mean values. Note the small mean decline in $Paco_2$ and the increase in Pao_2 in the patients with COPD while breathing on the mouthpiece. In contrast, the controls show a larger decline in $Paco_2$ and a much larger rise in Pao_2 with the same mouthpiece at rest. (Courtesy of Dr. J.D. Andrews.)

of exercise, a positive value for $P(a - ET)CO_2$ was rare. Predicting $PaCO_2$ from $PETCO_2$ is unlikely to be valid in patients with lung disease or with disorders affecting the ventilation–perfusion relationships.

More recently, Hansen et al.[51] studied the absolute values and relationships between mixed expired CO_2 ($P\bar{E}CO_2$) and end-tidal CO_2 ($PETCO_2$) during CPET in 100 individuals: 25 normal, 25 with chronic obstructive pulmonary disease (COPD), 25 with pulmonary arterial hypertension (PAH), and 25 with left ventricular heart failure. $PETCO_2$ was measured directly, whereas $P\bar{E}CO_2$ was calculated by dividing $VE/\dot{V}CO_2$ into 863. Their findings are summarized in Figure 7.11, which shows the successive mean changes in each group, from resting successively to end of unloaded cycling to *AT* to peak exercise. The most distinctive findings are the following:

1. At all stages of rest and exercise, absolute values of $P\bar{E}CO_2$ and $PETCO_2$ are highest in normal subjects (indicating good perfusion of the lung), intermediate in patients with COPD and LVF (indicating intermediate lung perfusion), and lowest in patients with PAH (indicating poor lung perfusion).
2. At all times, $P\bar{E}CO_2/PETCO_2$ ratios are lower in patients with COPD than all other groups, which indicates that patients with COPD have the largest percentages of slow-emptying airspaces during exhalations.
3. In all groups but patients with COPD, $PETCO_2$ decreases from the *AT* to peak exercise due to hyperventilation, which indicates that patients with COPD are generally unable to decrease their $PaCO_2$ and $[H^+]$ a in response to lactic acidosis.
4. In only patients with PAH, $PETCO_2$ values tend to decrease from rest to the *AT*, which indicates an inability to increase lung perfusion in proportion to the ventilatory stimulus from rest to the *AT*.
5. In patients with LHF, $PETCO_2$ values increase during the same period of time despite poor lung perfusion, which indicates that the ventilatory stimulus from rest to *AT* does not surpass the lung perfusion.

Although the mechanism(s) for the differences described in items 4 and 5 are not clear, the findings described help to noninvasively discriminate right ventricular failure due to primary pulmonary hypertension (pulmonary vasculopathy) from pulmonary hypertension secondary

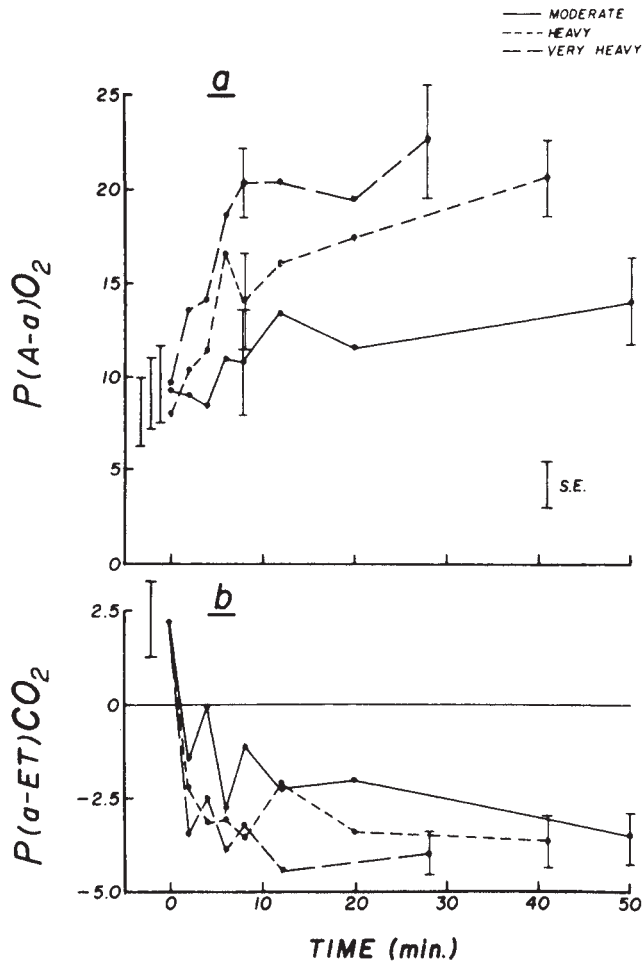

FIGURE 7.10. The $P(A-a)O_2$ and $P(a-ET)CO_2$ values in 10 normal young men at rest and during three intensities of cycle ergometer exercise as related to exercise duration. The mean and standard error of the mean (SEM) are depicted. (From Wasserman K, VanKessel A, Burton GB. Interaction of physiological mechanisms during exercise. *J Appl Physiol.* 1967;22:71–85, with permission.)

to LVF. In addition, it distinguishes those patients with ventilation/perfusion mismatch due to uneven ventilation (nonuniform airway time constants) from that due to nonuniform lung perfusion but with uniform airway time constants.

Recommendations

Normal values at sea level during upright exercise in adult men are as follows:

- P_{ACO_2}: Resting value = 36 to 42 mm Hg; stable or increasing slightly during mild and moderate exercise, decreasing with heavy exercise
- P_{ETCO_2}: Resting value = 36 to 42 mm Hg; increases normally by 3 to 8 mm Hg during mild and moderate exercise (depending on breathing pattern), and decreases with heavy exercise
- $P(a-ET)CO_2$ (mean ± SD) at the *AT* = –3 ± 3 mm Hg. At maximum exercise, the $P(a-ET)CO_2$ = –4 ± 3 mm Hg and is negative (P_{ETCO_2} exceeds P_{ACO_2}) in more than 95% of normal men.
- The changes in the absolute values of $P_{\bar{E}CO_2}$ and P_{ETCO_2} and their ratio during exercise are of diagnostic assistance in distinguishing patients with COPD, PAH, and LHF from normal subjects and each other.

Arterial, Alveolar, and End-Tidal Oxygen Tensions and Arterial Oxyhemoglobin Saturation

The normal resting P_{AO_2} is dependent on age, body position, and nutritional status, decreasing with age, obesity, fasting, and the supine position. Nevertheless, sea-level values less than 80 mm Hg are not seen in normal persons younger than 70 years in the sitting position except in those who are quite obese. The P_{ETO_2} and P_{AO_2} (the latter calculated from the alveolar gas equation; see Appendix C) are normally similar, but they may differ by 10 or more mm Hg in patients with severe maldistribution of ventilation. The P_{AO_2} and P_{AO_2} decrease, transiently, soon after the start of exercise (because the rise in $\dot{V}_E$ is slower than the rise in $\dot{V}O_2$, that is, respiratory exchange ratio [R] decreases) and then increase back to approximately resting values (see Chapter 2 on O_2 uptake kinetics).

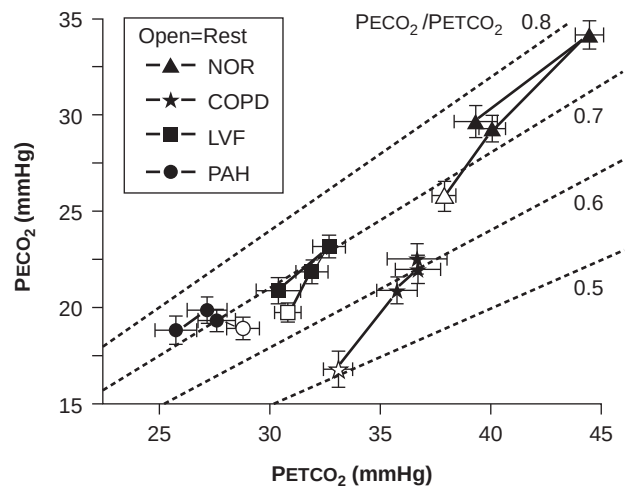

FIGURE 7.11. Mean and SEM values of mixed expired CO_2 (P_{ECO_2}), end-tidal CO_2 (P_{ETCO_2}), in mm Hg are shown for four groups: normal (NOR), chronic obstructive pulmonary disease (COPD), left ventricular failure (LVF), and pulmonary arterial hypertension (PAH). The open symbols are resting values; the solid symbols represent a progression at end of warmup period, at *AT*, and at end of exercise. The dashed diagonal lines indicate the P_{ECO_2}/P_{ETCO_2} ratios from 0.5 to 0.8. See text for further interpretation. (From Hansen J, Ulubay G, Chow BF, et al. Mixed-expired and end-tidal CO_2 distinguish between ventilation and perfusion defects during exercise testing in patients with lung and heart diseases. *Chest.* 2007;132:977–983, with permission.)

The arterial oxyhemoglobin saturation (Sa_{O_2}) normally changes less than 2% from rest to maximal exercise. In highly motivated athletes, the Sa_{O_2} has been reported to fall below resting values,[39] but this is uncommon.

The $P_{ET}O_2$ normally increases 10 to 30 mm Hg for exercise above the *AT* because of metabolic acidosis–induced hyperventilation, rising R and high ratio ventilation-perfusion mismatching at maximal exercise.

Many reports show that the $P(A-a)O_2$ increases during heavy exercise in normal subjects. Lilienthal et al.[71] and Asmussen and Nielsen[6] found a mean $P(A-a)O_2$ of 30 mm Hg at high work rates. In 17 normal active men not in physical training, Jones et al.[63] found a mean $P(A-a)O_2$ of 12 mm Hg at rest, with an increase to approximately 20 mm Hg at work rates with a $\dot{V}O_2$ over 1.5 L/min. In five healthy young men, Whipp and Wasserman[110] found a $P(A-a)O_2$ of 7.4 ± 4.2 mm Hg (mean ± SD) at rest and 10.8 ± 3.6 mm Hg at heavy exercise. Cruz et al.[32] studied four subjects at rest and at work rates approximating 50%, 75%, and 100% of peak $\dot{V}O_2$ at sea level and found $P(A-a)O_2$ values of 11.5 ± 5.4, 11.0 ± 4.2, 16.3 ± 2.6, and 20 ± 8.8 mm Hg, respectively. Hansen et al.[56] studied 16 healthy young men, aged 18 to 24, during sea-level exercise on a cycle ergometer and found that the mean $P(A-a)O_2$ was 8 mm Hg while sitting at rest, 7 mm Hg during mild exercise, 11 mm Hg during moderate exercise, and 15 mm Hg during maximum exercise.

Similar results were obtained by Wasserman et al.[106] in 10 healthy young men; values are shown at rest and at three work intensities as related to time in Figure 7.10. In 77 normal older men (aged 34 to 74 years), we found $P(A-a)O_2$ values (mean ± SD) of 12.8 ± 7.4 mm Hg at rest and 19.0 ± 8.8 mm Hg at maximum exercise.[55,93] At maximum exercise, $P(A-a)O_2$ was greater than 35 mm Hg in only 3 of these 77 men.

Recommendations

The normal arterial blood and $P_{ET}O_2$ values at sea level during upright exercise in adult men are as follows:

- Free-flowing capillary blood P_{O_2} values are usually 5 to 10 mm Hg less than concurrently measured Pa_{O_2}, but the differences are variable and technique dependent.
- Pa_{O_2} at rest = 80 mm Hg or greater; usually increases slightly with heavy exercise
- Sa_{O_2} at rest = 95% or greater; no decrease with exercise
- $P_{ET}O_2$ at rest = 90 mm Hg or greater; increases with heavy exercise
- $P(A-a)O_2$ (mean ± SD) for ages 20 to 39 years: At rest = 8 mm Hg, at the *AT* = 11 mm Hg, and at maximum exercise = 15 mm Hg
- $P(A-a)O_2$ (mean ± SD) for ages 40 to 69 years: At rest = 13 ± 7 mm Hg, at the *AT* = 17 ± 7 mm Hg, and at maximum exercise = 19 ± 9 mm Hg
  The upper limit of normal (95% confidence level) at the *AT* = 28 mm Hg and at maximum exercise = 35 mm Hg

Femoral and Mixed Venous Values and Estimation of Cardiac Output

Muscle blood flow and oxygen extraction both increase strikingly with exercise. At near-maximum leg exercise, femoral vein values in normal subjects reach the following mean ± SE values: P_{O_2} = 20 ± 2 mm Hg, S_{O_2} = 17% ± 3%, pH = 7.00 ± 0.04, P_{CO_2} = 80 ± 5 mm Hg, and lactate = 10 ± 1 mmol/L. In patients with heart disease, minimum mean femoral vein values are similar: P_{O_2} = 18 mm Hg and S_{O_2} = 18% to 21%. Concurrent mixed venous values in the same patients are 2 mm Hg and 4% higher, respectively.

The usual values found for mixed venous S_{O_2} ($S\bar{v}o_2$) at peak treadmill or cycle exercise approximate 25%. In normal subjects, as well as in patients with heart failure, $S\bar{v}o_2$, $C\bar{v}o_2$, $C(a-\bar{v})O_2$, and O_2 extraction ratio [$C(a-\bar{v})O_2/Cao_2$] change in relatively linear fashion as $\dot{V}O_2$ changes from rest to peak values. In five normal men, the $C(a-\bar{v})O_2$ values (in mL/100 mL blood) were 5.72 + 0.1 × % peak $\dot{V}O_2$, with a standard deviation of 1.08 mL/100 mL, r = 0.94. Combining the data from three studies involving normal subjects and patients with congestive heart failure,[92,95,109] the $C(a-\bar{v})O_2$ values (in mL/100 mL blood) were 5.55 + 0.085 × % peak $\dot{V}O_2$, with a standard deviation of 1.09, r = 0.97. Absolute Cao_2 values are dependent on the hemoglobin concentration, which usually rises 5% to 8% at peak exercise in healthy individuals.

Historically, it has been suggested that cardiac output could be measured noninvasively during exercise with the Fick principle by estimating mixed venous CO_2 content using rebreathing techniques.[61] This method for estimating cardiac output depends on the premise that mixed venous P_{CO_2} values are highly correlated with mixed venous CO_2 content. This is not the case, as shown in Chapter 3.

Recommendations

- In the normal person and the patient with heart disease, femoral vein mean ± standard error values are P_{O_2} = 19 ± 3 mm Hg and S_{O_2} = 19% ± 3% at maximum leg exercise, when such exercise is not limited by other than cardiovascular factors.
- Concurrent mixed venous values are P_{O_2} = 21 ± 3 mm Hg and S_{O_2} = 23% ± 3%. In such individuals, the $S\bar{v}o_2$, $C\bar{v}o_2$, $C(a-\bar{v})O_2$, and O_2 extraction ratio change in near linear fashion from rest to maximum exercise.
- In the absence of anemia, hypoxemia, or significant carboxyhemoglobinemia, $C(a-\bar{v})O_2$ in mL/100 mL of blood is 5.55 + 0.085 × peak $\dot{V}O_2$ with an SD = 1.1 mL/100 mL blood. These values can be used to estimate cardiac output and stroke volume, especially at maximum exercise.[1]

Acid–Base Balance

In the normal individual, an intense metabolic acidosis is induced by heavy exercise (see Chapters 2 and 3). Measurement of the acid–base status at the termination

of an incremental exercise test is valuable in deciding whether the subject has made a good effort and performed near maximum exercise. Resting venous and arterial lactate values are normally less than 1 mmol/L and typically rise substantially before the termination of maximal exercise. During exercise, venous lactate values can be dependent on the site of lactate production and the sampling site,[109] whereas arterial or mixed venous lactate values give a better indication of the total body lactate burden.

As previously described, the rise in blood lactate during exercise is accompanied by a nearly equimolar decline in bicarbonate and a decrease in pH. This metabolic acidosis stimulates ventilation, decreasing Pa_{CO_2}, and increasing $\dot{V}_{CO_2}$ beyond that predicted from aerobic metabolism. This is reflected by an increase in R due to extra CO_2 generated by HCO_3^- buffering of lactic acid. The arterial lactate and R reach their peak and the pH and bicarbonate reach their nadir at about 2 minutes into recovery (Table 7.7). The magnitudes of the lactate and bicarbonate changes indicate the severity of exercise-induced metabolic acidosis.

Normal values for younger[17] and older[55] men for incremental cycle exercise tests are given in Table 7.7. Small changes signify a mild degree of exercise stress secondary to low motivation or disorders that preclude the performance of exercise at a significant level above the *AT*.

Recommendations

- R values (mean ± SD) in normal older men at end of exercise are 1.21 ± 0.12 and are 1.59 ± 0.19 at 2 minutes of recovery. However, the value of R depends on the rate at which lactate increases and HCO_3^- decreases, not on the work rate per se.
- Decline in HCO_3^- and increase in lactate (both in mmol/L) at end of exercise are approximately 6 ± 2 in younger men and 4 ± 2.5 in older men; at 2 minutes of recovery, these are approximately 8.4 ± 2.5 in all men.

PREDICTED VALUES FOR CHILDREN

Peak Oxygen Uptake

Normal values for maximal exercise tests are obtained from studies done on large samples of healthy children. These values are effort dependent. Healthy subjects may be cajoled and prodded to continue exercising in the high-intensity range in order to achieve data of optimal quality. In contrast, patients with known or even suspected abnormalities should not be encouraged as vigorously as healthy subjects. As a consequence, maximal values for children with suspected impairments may be underestimated, when compared with the maximal values for presumed normal children.

Although sustained heavy exercise rarely occurs in children, traditional exercise testing focuses largely on the peak or maximal oxygen uptake ($\dot{V}_{O_2}$max), which can only be measured from sustained exercise precisely in the high-intensity range. $\dot{V}_{O_2}$max probably occurs only in the confines of the exercise laboratory, and a "true" $\dot{V}_{O_2}$max (i.e., a plateau in $\dot{V}_{O_2}$ while the work rate continues to increase) is observed in only about 28% of children and adolescents.[29] Because of this, CPET in children includes a growing variety of less effort dependent and less quantitative protocols, like physical work capacity (PWC) at a specified HR. In the PWC testing paradigm,[42,43,99] the subject performs a progressive exercise test in which the main variable is the work rate achieved at a specified submaximal HR (usually around 150–170 bpm). The PWC has been used in a number of

Table 7.7

Metabolic Acidosis at the End of and during Recovery from Maximum Incremental Cycle Ergometer Exercise in Normal Sedentary Men

	At End of Exercise		2 Minutes into Recovery	
Age (year)	18–24	34–74	18–24	34–74
Number studied	10	77	10	77
Average exercise duration (min)	18	9	18	9
Arterial lactate increase (mmol/L)[a]	6.6 ± 1.4	—	7.6 ± 1.8	—
Arterial HCO_3^- decrease from rest (mmol/L)[a]	6.2 ± 2.3	4.0 ± 2.5	8.7 ± 2.6	8.5 ± 2.9
Arterial pH[a]	7.31 ± 0.04	7.37 ± 0.04	7.29 ± 0.04	7.33 ± 0.03
Gas exchange ratio (R)[a]	—	1.21 ± 0.12	—	1.59 ± 0.19

[a]Values are means ± standard deviation.

(Data are from Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis.* 1984;129(pt 2):S49–S55; Beaver WL, Wasserman K, Whipp BJ. Bicarbonate buffering of lactic acid generated during exercise. *J Appl Physiol.* 1986;60:472–478.)

studies of exercise and pediatric lung diseases such as asthma and cystic fibrosis.[15,82] Other submaximal approaches to exercise testing that are more amenable to field studies, such as the 20-meter shuttle run and the 6-minute walk per run test, have also been used to assess fitness in children with a variety of lung diseases and pulmonary hypertension.[4,45,67–69]

A reduction in physical activity has become apparent worldwide over the past several decades,[98] which is a worrisome trend. Here, we present measurements of aerobic function for children in our environment. Ideally, each laboratory should compare a sample of local, healthy children to help choose an appropriate set of normal values relative to those presented here. Some relatively large-sample normative values for children are included in the references.[73,83,97,100]

Cooper et al.[28,29] reported peak $\dot{V}O_2$ for 109 children, aged 6 to 17 years, who performed cycle ergometry using a continuously increasing work rate protocol. Because these subjects were not obese, peak $\dot{V}O_2$ correlated similarly with either weight or height (Fig. 7.12). The prediction equations are as follows:

For normal boys: Peak $\dot{V}O_2$ (mL/min) = 52.8 × weight − 303.4
$r = 0.94$

For normal girls: Peak $\dot{V}O_2$ (mL/min) = 28.5 × weight + 288.2
$r = 0.84$

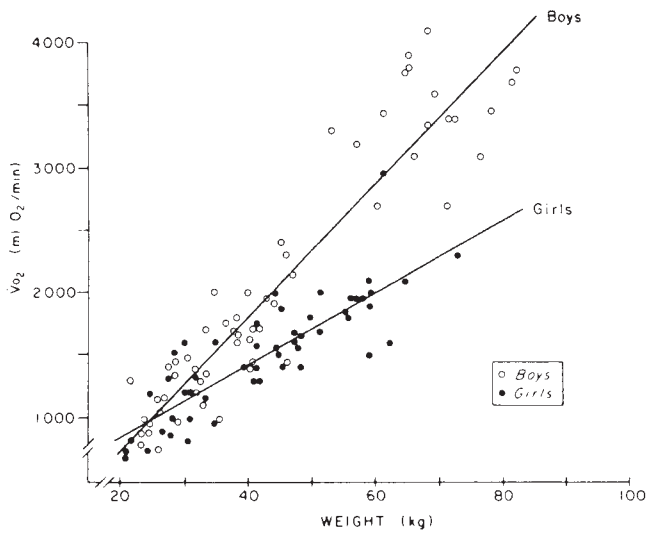

FIGURE 7.12. Peak $\dot{V}O_2$ of 109 normal North American boys and girls for leg cycling. Regression equations for peak $\dot{V}O_2$ (mL/min) as function of body weight (kg) were as follows: for boys, $\dot{V}O_2 = 52.8 \times \text{weight} - 303$ ($r = 0.94$); for girls, $\dot{V}O_2 = 28.5 \times \text{weight} + 288$ ($r = 0.84$). (From Cooper DM, Weiler-Ravell D, Whipp BJ, et al. Aerobic parameters of exercise as a function of body size during growth in children. *J Appl Physiol.* 1984;56:628–634, with permission.)

These prediction equations are similar to those of Astrand[7] for the boys, but that the girls studied by Astrand had a significantly higher $\dot{V}O_2$max versus height relationship. Cooper et al.[29] suggested that cultural or societal differences might account for this difference observed in girls.

Recommendations

- Recommended mean values for peak $\dot{V}O_2$ for children of average activity levels performing cycle ergometry are:

For normal boys: Peak $\dot{V}O_2$ (mL/min) = 52.8 × weight − 303.4
$r = 0.94$

For normal girls: Peak $\dot{V}O_2$ (mL/min) = 28.5 × weight + 288.2
$r = 0.84$

The primary data and correlations for predicted peak $\dot{V}O_2$ for leg cycling for children are shown in Figure 7.12.

- For overweight patients, increase the predicted peak $\dot{V}O_2$ by 6 mL/min for each kilogram of weight above normal (predicted) weight.

Peak Heart Rate and Heart Rate Reserve

The maximum or peak HR achieved declines with age in all studies. No consistent differences have been found between boys and girls or among the types of exercise used (e.g., leg cycling, stepping, inclined treadmill, walking, running). Scandinavian children were found to have an average peak HR of 205 bpm,[10] whereas North American children aged 8 to 18 years had an average peak HR of 187 bpm, with a lower 95% confidence limit of 160.[97]

The concept of HRR can be useful for estimating the relative stress of the cardiovascular system during exercise, but it should be used with caution. A normal HRR is zero. The mean predicted peak HR may not be reached because of normal population variability, poor motivation, medications such as β-adrenergic blockers, or because of heart, peripheral vascular, lung, endocrine, or musculoskeletal diseases.

Recommendations

Peak HR values should be measured and averaged at the same time as the peak $\dot{V}O_2$ values. The following equations can be used to estimate the predicted peak HR and the HRR for adults and children:

- Predicted peak HR (beats/min) = 220 − age (years)
- HRR = Predicted peak HR − Observed peak HR

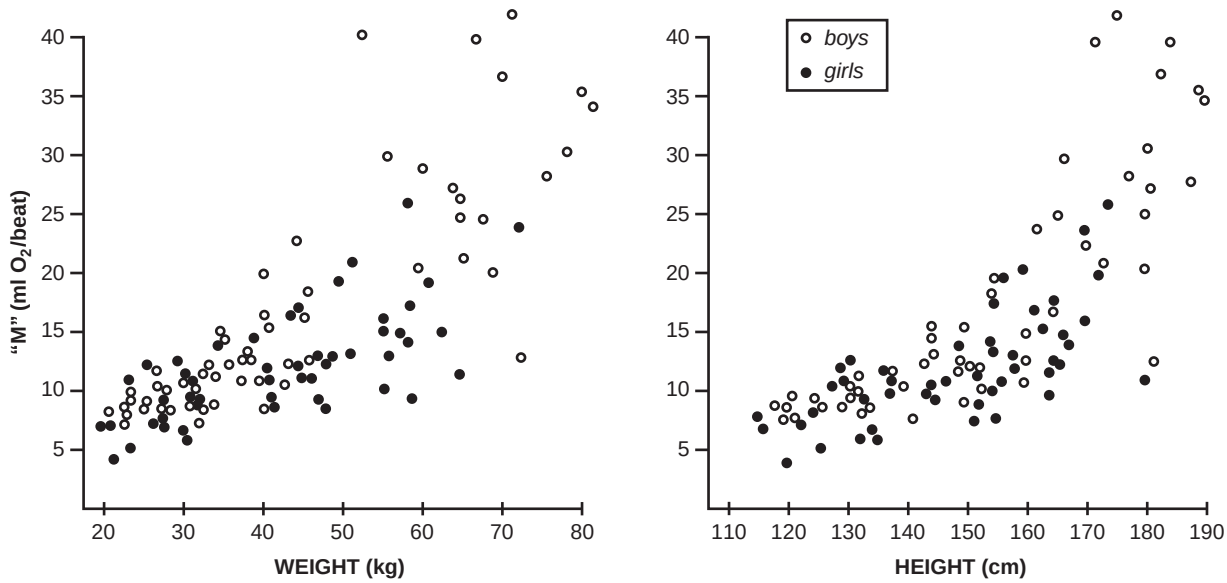

FIGURE 7.13. The slope *M* of the $\dot{V}O_2$-HR relationship as a function of body weight (*left panel*) and height (*right panel*) in the study population. The slope increased systematically with increasing body size, but more rapidly in boys than in girls. Using height, the linear regression equation was: $M = 0.32(Ht) - 33.9$, $r = 076$, for the whole study population. (From Cooper DM, Weiler-Ravell D, Whipp BJ, et al. Growth-related changes in oxygen uptake and heart rate during progressive exercise in children. *Pediatr Res.* 1984;18:845–851, with permission.)

Relationship of Oxygen Uptake and Heart Rate: The Peak Oxygen Pulse

In a given individual, a consistent relationship exists between $\dot{V}O_2$ and HR during exercise. The quotient of the $\dot{V}O_2$ and HR is the O_2 pulse; its values are dependent on the stroke volume and the difference between the arterial and mixed venous blood O_2 content. The arteriovenous O_2 difference is, in turn, dependent on the availability of hemoglobin, blood oxygenation in the lung, and extraction of oxygen in the periphery.

Cooper et al.[29] related the slope of the $\dot{V}O_2$ to HR to weight and height for boys and girls (Fig. 7.13). The slope gets steeper with growth. When normalized to weight, there is no systematic change in slope of $\dot{V}O_2$ versus HR with aging (Fig. 7.14). However, past puberty, the slope of $\dot{V}O_2$ versus HR for boys is steeper than that for girls. The peak O_2 pulse for boys and girls as related to size is shown in Figure 7.15.

Recommendations

See Figures 7.13 and 7.14 and Cooper et al.[29] for slope of $\dot{V}O_2$–HR relationship. See Figure 7.15 for predicted peak O_2 pulse.

Anaerobic Threshold

Cooper et al.[27] tested 51 girls and 58 boys between the ages of 6 and 17 years. The subjects were healthy and nonobese but did not participate in vigorous sports. Mean *AT* was 58% of peak $\dot{V}O_2$, and the lower limit of normal for this sample of normal children was 44% of peak $\dot{V}O_2$ (Fig. 7.16). Comparative values for *AT* in children with a variety of disease states, such as cerebral palsy[101] and congenital heart disease,[85] are also available.

Recommendations

The mean values and confidence limits for the predicted *AT* in normal children are given in Table 7.8, with the

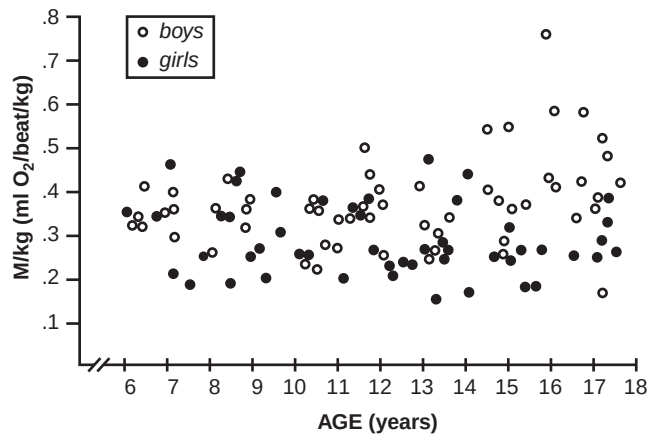

FIGURE 7.14. The slope *M* of the $\dot{V}O_2$–HR relationship normalized for body weight: (*M*/kg) as a function of age. There was no systemic change for *M*/kg in the population as a whole, but values for boys were significantly higher than for girls. (From Cooper DM, Weiler-Ravell D, Whipp BJ, et al. Growth-related changes in oxygen uptake and heart rate during progressive exercise in children. *Pediatr Res.* 1984;18: 845–851, with permission.)

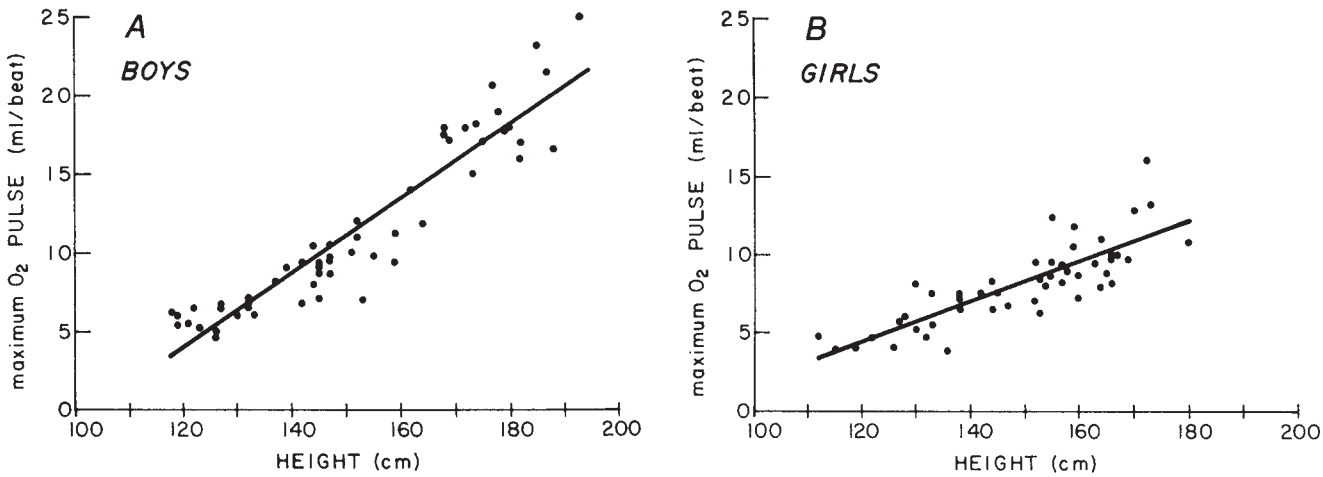

FIGURE 7.15. Maximum O_2 pulse for normal North American boys (**A**) and girls (**B**). For boys, the best-fit regression line is O_2 pulse (mL/beat) = 0.23 × height (cm) − 24.4. The lower 95% confidence limit is 3.8 mL/beat below the regression line. For girls, the equation is O_2 pulse (mL/beat) = 0.128 × height (cm) − 10.9 with a lower 95% confidence limit of 3.0 mL/beat below the regression line. (Modified from Cooper DM, Weiler-Ravell D, Whipp BJ, et al. Growth-related changes in oxygen uptake and heart rate during progressive exercise in children. *Pediatr Res.* 1984;18:845–851.)

ratios of predicted *AT* to predicted peak $\dot{V}O_2$ in Figure 7.16. It can be seen in the latter that the lower 95% confidence limit for the ratio of predicted *AT* to predicted peak $\dot{V}O_2$ is about 44%.

Oxygen Uptake–Work Rate Relationship

When a progressively increasing work rate test is initiated, a delay occurs before oxygen uptake begins to increase in a linear fashion. This delay must be considered in the calculation of the overall value of the oxygen uptake–work rate relationship ($\Delta\dot{V}O_2/\Delta WR$). This kinetic delay is equal to the time constant of $\dot{V}O_2$ following a stepwise increase, is accounted for by the kinetics of muscle O_2 utilization, and is normally between one-half and three-quarters of a minute. Thus, the formula used to calculate $\Delta\dot{V}O_2/\Delta WR$ is the following:

$$\Delta\dot{V}O_2/\Delta WR = (\text{Peak } \dot{V}O_2 - \text{Unloaded } \dot{V}O_2)/[(T - 0.75) \times S]$$

where $\dot{V}O_2$ is measured in milliliters per minute, T is the time of incremental exercise, and S is the slope of work rate increment in watts per minute.[54] There has been a renewed interest in the oxygen uptake–work rate relationship in children. In a recent study, for example, Groen et al.[49] studied children with both respiratory and vascular diseases and concluded that:

> $\Delta\dot{V}O_2/\Delta WR$ may be more sensitive for conditions that are characterized by local hypoperfusion (as in juvenile dermatomyositis), than for conditions that are characterized by impaired oxygen delivery.

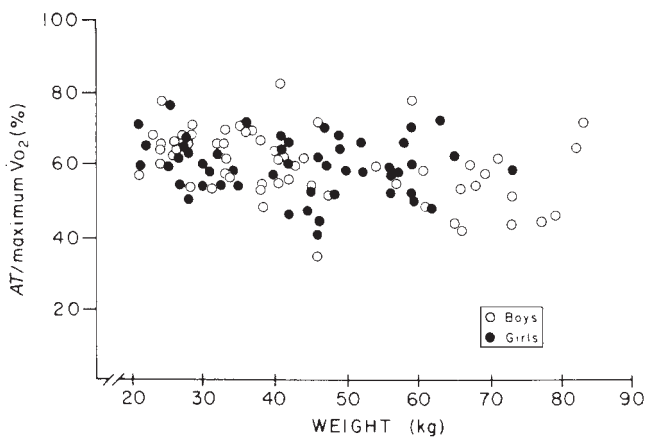

FIGURE 7.16. The ratio of anaerobic threshold to peak $\dot{V}O_2$ (*AT*/maximum $\dot{V}O_2$), as a percentage, for 109 normal North American boys and girls. (From Cooper DM, Weiler-Ravell D, Whipp BJ, et al. Aerobic parameters of exercise as a function of body size during growth in children. *J Appl Physiol.* 1984;56:628–634, with permission.)

Ventilatory Efficiency

There is a linear relationship between $\dot{V}E$ and $\dot{V}CO_2$ for most of the progressively increasing work rate test.[26] Factors such as elevated $PaCO_2$ will tend to lower the magnitude of the slope while a high V_D/V_T will render the slope steeper. We and others have found it helpful to quantify the relationship between $\dot{V}E$ and $\dot{V}CO_2$ by calculating the slope of the best fit line through the linear portion of the relationship. Normal values have now been established for this parameter.[50,74,75] The slope of the relationship ($\Delta\dot{V}E/\Delta\dot{V}CO_2$) decreases with increasing size among children and teenagers (Fig. 7.17). Younger children need to breathe more than adults for a given increase in metabolic rate (i.e., $\Delta\dot{V}CO_2$). Whether this results from a lower $PaCO_2$ or a higher V_D/V_T with lower body size has not yet been determined.[5,14,81] However, the range of $\Delta\dot{V}E/\Delta\dot{V}CO_2$ values average 26 for a 20-kg child and 20 for an 80-kg child.

Table 7.8

Predicted Peak $\dot{V}O_2$ and Anaerobic Threshold in Normal Children for Cycle Ergometry

	Boys		Girls	
Age	≤13 years	>13 years	≤11 years	>11 years
Number studied	37	21	24	27
Peak $\dot{V}O_2$, mL/min/kg (mean ± SD)	42 ± 6	50 ± 8	38 ± 7	34 ± 4
Lower 95% confidence limit	32	37	26	27
Anaerobic threshold, mL/min/kg (mean ± SD)	26 ± 5	27 ± 6	23 ± 4	19 ± 3
Lower 95% confidence limit	18	17	16	14

SD, standard deviation.
(From Cooper DM, Weiler-Ravell D. Gas exchange response to exercise in children. *Am Rev Respir Dis.* 1984;129(pt 2):S47–S48, with permission.)

Additional data demonstrate substantial differences between children and adults in the $\dot{V}E$ and $\dot{V}CO_2$ responses to and recovery from 1 minute of high-intensity exercise.[4] We used these short exercise protocols because they more closely mimic patterns of activity actually observed in real life in children. Adults took longer than did children to recover from exercise, and $\tau\dot{V}CO_2$ (τ is the recovery time constant; the time required to reach 63% of the end-exercise to pre-exercise steady-state values) and $\tau\dot{V}E$ increased with work intensity in adults but not in children. These results are consistent with the hypothesis of a reduced anaerobic capability in children (see below). If high-intensity exercise in children results in a smaller increase in lactic acid concentrations, then less CO_2 will be produced from bicarbonate buffering of hydrogen ion.

$PaCO_2$ seems to be controlled at lower levels in children compared with adults.[20,21,91] These observations were corroborated indirectly by the measurements of end-tidal PCO_2 ($PETCO_2$) made in our 1-minute exercise studies showing that pre-exercise and peak-exercise values were significantly lower in children compared with adults, and more directly in a study of arterial $PaCO_2$ in children by Ohuchi et al.[81] A lower CO_2 set point may also explain, in part, the greater slopes of the $\dot{V}E$-$\dot{V}CO_2$ relationship that we and others[79] observed in progressive exercise tests; if alveolar PCO_2 is lower, then more $\dot{V}E$ is needed to excrete a given amount of CO_2.

The coupling of $\dot{V}CO_2$ and $\dot{V}E$ is closer in children than in adults. The rise in $PETCO_2$ with exercise seen in both children and adults indicates that $\dot{V}CO_2$ increased more rapidly than $\dot{V}E$, but the exercise-induced increase in $PETCO_2$ was much smaller in children (from 37.8 ± 0.4 to 40.1 ± 0.3 mm Hg) compared to adults (from 40.5 ± 0.2 to 49.9 ± 0.4), suggesting that $\dot{V}E$ kept pace with $\dot{V}CO_2$ better in children than in adults during exercise and early in recovery. Ratel et al. explored the implications of this close coupling on acid–base balance during exercise in children.[84]

While recovery $\tau\dot{V}E$ was significantly longer than $\tau\dot{V}CO_2$ in adults following 1 minute of high-intensity exercise, the recovery times for $\dot{V}E$ and $\dot{V}CO_2$ were indistinguishable in the children.

Recommendations

Normal values for $\dot{V}E/\dot{V}CO_2$ and $\dot{V}E$ versus $\dot{V}CO_2$ below the respiratory compensation point (with $\dot{V}E$ expressed as L/min BTPS and $\dot{V}CO_2$ as L/min STPD) for cycle or treadmill ergometry are given in Figure 7.17 and Cooper et al.[26]

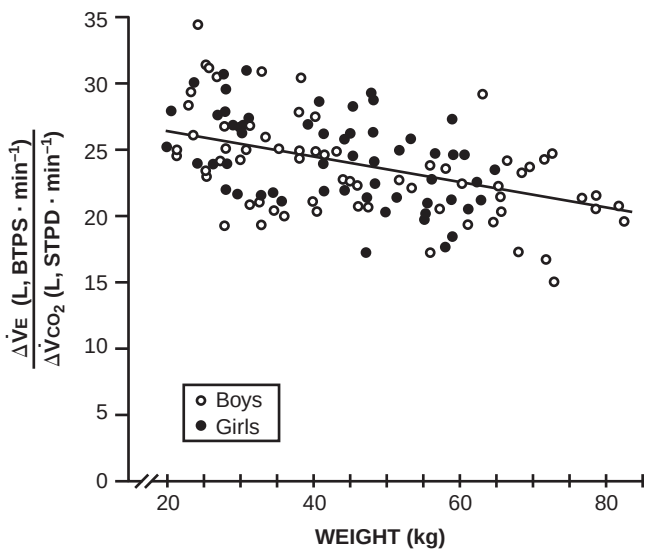

FIGURE 7.17. Slope of the $\dot{V}E$-$\dot{V}CO_2$ relationship as a function of body weight in 128 normal subjects ranging in age from 6 to 18 yr. Boys are represented by open circles; girls by closed circles. There was a small but significant negative correlation between the slope and body weight. (From Cooper DM, Kaplan MR, Baumgarten L, et al. Coupling of ventilation and CO_2 production during exercise in children. *Pediatr Res.* 1987;21:568–572, with permission.)

SUMMARY

This chapter presented and critiqued absolute values and patterns of change during CPET from rest to peak exercise and through recovery for a number of variables, including $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, HR, blood pressure, end-tidal CO_2 and O_2, as well as arterial blood O_2, CO_2, and $[H^+]$ values. Also considered were the *AT*, O_2 pulse, $\Delta\dot{V}O_2/\Delta WR$, $\Delta\dot{V}O_2/\Delta HR$, VD/VT, $\dot{V}CO_2$, and $\dot{V}O_2$ values in adults and children.

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CHAPTER

8

Diagnostic Specificity of Exercise Intolerance: A Flowchart Approach

INTRODUCTION TO FLOWCHARTS

When patients complain of exercise intolerance, it is usually because they are unable to accomplish a task that they expect to complete with comparative ease and without unusual effort or undue feelings of fatigue or shortness of breath. Identifying the cause of exercise intolerance is one of the major objectives of integrative cardiopulmonary exercise testing.

The measurements needed for physiological assessment are discussed in Chapter 4, and their patterns of change in response to the pathophysiology of specific diseases are described in Chapter 5 and further in Chapters 9 and 10. Once the optimal exercise protocol is chosen (see Chapter 6) and the predicted values are selected for the discriminating physiological variables (see Chapter 7), the task of identifying the probable cause(s) of the exercise intolerance still remains. This chapter introduces a flowchart strategy to show how the measurements made during exercise may be used to deduce, systematically, the potential pathophysiology likely to be seen in specific diseases. Although the analytic method presented here is not necessarily ideal in all instances, the flowcharts serve as a structure for interpreting cardiopulmonary exercise tests. They provide a foundation for reaching a physiologically based interpretation of exercise intolerance, as well as focusing on the physiological variables that reflect the pathophysiology of different clinical disorders.

To facilitate description of each decision based on physiological measurements, each decision branch point is numbered on the flowcharts. The letter *R* refers to the right branch of the numbered branch point, and *L* to the left branch. Each final branch point leads to a box containing a diagnosis that can account for the parameters or measurements found in the decision-making process. Under the diagnosis is a list of additional measurements that further support the diagnosis. The branch points were developed as dichotomous choices that facilitate decision making. However, each branch-point decision and choice of which flowchart to use for diagnostic analysis should not be rigidly applied. If the physiological variable addressed at a particular branch point does not strongly favor one or the other branch, or if the measurements described in the diagnosis box do not consistently support

that diagnosis, both branches of a branch point should be considered. Thus, the flowcharts should be used with some degree of flexibility and consideration of sound physiological principles.

ESTABLISHING THE PATHOPHYSIOLOGICAL BASIS OF EXERCISE INTOLERANCE

The first question to address is whether the peak $\dot{V}O_2$ is normal or decreased, thereby establishing if the patient has exercise intolerance. The second question is whether the anaerobic threshold (*AT*) is normal or decreased. The answers to these two questions lead the interpreter to a subsequent flowchart, which further focuses on the diagnostic possibilities. Other measurements then lead to the single pathophysiological state most consistent with the exercise data. From knowledge of the pathophysiological state, anatomical correlates may be sought, if deemed necessary, through other studies.

We equate *AT* to lactic acidosis threshold (*LAT*) in the flowcharts. The *AT* is the physiological identification of the onset of anaerobic glycolysis that supports aerobic glycolysis for adenosine triphosphate (ATP) regeneration, and that the critical capillary P_{O_2} had been reached, in progressively increasing work rate exercise testing. It is the conceptual definition of the gas exchange changes that accompany the onset of the exercise lactic acidosis. The *LAT* implies that lactate and arterial acid–base balance were measured. Otherwise, *AT* and *LAT* are the same.

In the flowcharts, the patient's peak $\dot{V}O_2$ is related to the predicted peak $\dot{V}O_2$ or $\dot{V}O_2$max values provided in Chapter 7. Thus, a reduced peak $\dot{V}O_2$ identified at the start of Flowcharts 3 to 5 means that the value is below the 95% confidence limits of the predicted peak $\dot{V}O_2$.

PEAK $\dot{V}O_2$ AND ANAEROBIC THRESHOLD (FLOWCHART 1)

Analysis of data obtained during the exercise test begins in Flowchart 1 (Fig. 8.1), which separates patients based on their measured peak $\dot{V}O_2$ and *AT*. Patients are divided into those with normal or reduced peak $\dot{V}O_2$. Patients are further divided into those with normal, reduced, or

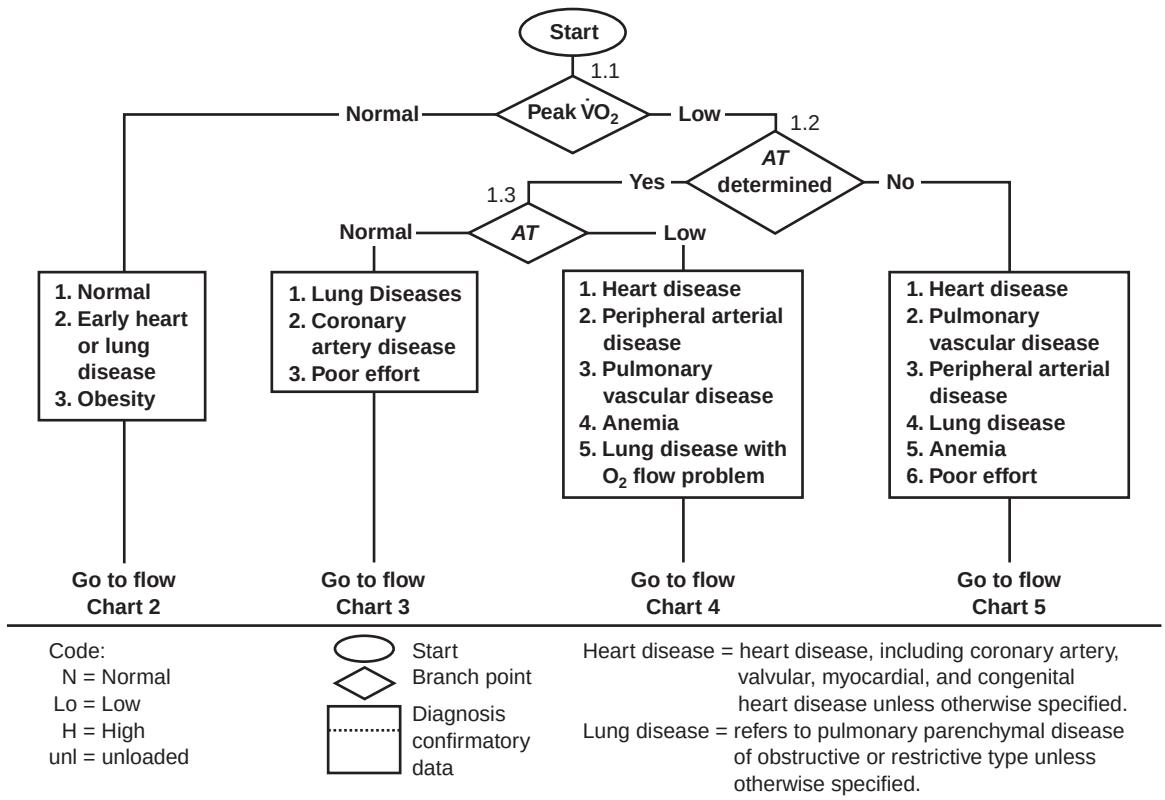

FIGURE 8.1. Flowchart 1 for the differential diagnosis of the cause of exercise limitation. Analysis starts with the measurement of peak $\dot{V}O_2$. *Ellipsoids* indicate starting points, highlighting a question. The *diamonds* indicate branch points in the decision logic based on further questions. The *boxes* provide potential diagnoses (listed above the horizontal dashed line) and measurements that support the diagnosis (below the horizontal dashed line). If the supporting measurements do not fit well, try a closely related branch point leading to a different diagnosis in which the supporting measurements fit better. Branch points are numbered to correspond to the text. The codes shown at the bottom of this figure pertain to all five flowcharts.

indeterminate *AT*. The analysis then proceeds to one of four other flowcharts (Flowcharts 2 to 5; see Figs. 8.2 to 8.5) for each of these groups.

Only a few conditions are associated with subjective exercise intolerance and normal peak $\dot{V}O_2$; these are considered in Flowchart 2 (see Fig. 8.2). A low peak $\dot{V}O_2$, with a normal *AT*, suggests that O_2 flow at a submaximal exercise level is within normal limits, but maximum exercise capacity is limited by one of a variety of other causes, as shown in Flowchart 3 (see Fig. 8.3). The combination of both low peak $\dot{V}O_2$ and low *AT* leads to Flowchart 4 (see Fig. 8.4), in which disorders that limit the capacity to transport oxygen are described. Finally, the *AT* may not always be identified because of poor patient effort, artifacts of measurement, or an inappropriate work rate protocol. A diagnostic scheme for use when the *AT* is not identified is outlined in Flowchart 5 (see Fig. 8.5).

EXERCISE INTOLERANCE WITH NORMAL PEAK OXYGEN UPTAKE (FLOWCHART 2)

When peak $\dot{V}O_2$ is normal but the patient complains of exercise intolerance, the diagnostic possibilities are as follows:

1. The patient is normal but has anxiety about failing health or decreased fitness.
2. The patient is obese to the point of requiring an increased metabolic and cardiopulmonary response to perform activity.
3. The patient, previously healthy, has developed early cardiovascular or lung disease. Thus, despite a reduced ability to do the physical work to which he or she is accustomed, the peak $\dot{V}O_2$ still falls within the normal range of the subject's predicted peak $\dot{V}O_2$.

The diagnostic flowchart leading to each of these diagnoses is shown in Figure 8.2.

A normal peak $\dot{V}O_2$ (equal to the predicted peak $\dot{V}O_2$), with a low *AT*, is unusual in normal subjects. However, it might be found in exceptionally sedentary subjects or patients with very mild disease that compromises O_2 transport to muscle cells.

Normal Individual with Anxiety State (Branch Points 2.1-L and 2.2-L)

People anxious about their health tend to be physically active and try to maintain their general state of health; otherwise, they would not be concerned. Therefore, their peak $\dot{V}O_2$ is generally on the high side of normal and they are not obese. If the exercise electrocardiogram (ECG), O_2 pulse, and arterial blood gas values are normal at all work rates, including the peak, the patient is probably normal. The breathing reserve should also be normal. However,

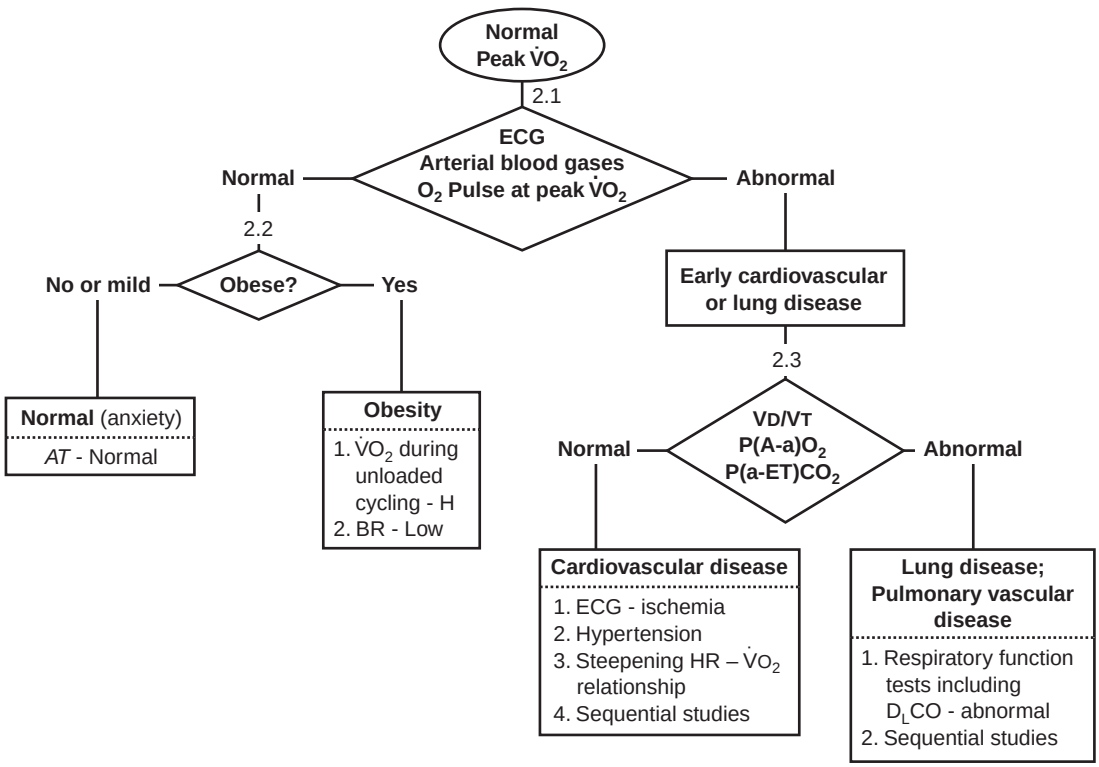

FIGURE 8.2. Flowchart 2 for conditions in which peak $\dot{V}O_2$ is normal but the patient feels limited during exercise. If the supporting measurements do not fit well, try a closely related branch point leading to a different diagnosis in which the confirmatory measurements fit better. Symbols and use of flowchart are as described in "Introduction to Flowcharts" and Figure 8.1.

the peak $\dot{V}O_2$ may be on the low side of normal if the subject had a high peak $\dot{V}O_2$ that was originally considerably better than the predicted normal value. A confirmatory measurement is a normal *AT* that is above the mean predicted value. A patient with these findings would benefit from reassurance (see Cases 1 and 9 in Chapter 10).

Obesity (Branch Points 2.1-L and 2.2-R)

Obese subjects require an increased metabolic rate ($\dot{V}O_2$ and $\dot{V}CO_2$) to perform a given physical activity compared with nonobese subjects. The increased metabolic rate mandates an increased cardiac output [cardiac output = $\dot{V}O_2/C(a - \bar{v})O_2$] and minute ventilation ($\dot{V}E = \dot{V}CO_2/[(1 - VD/VT) \times (PaCO_2/PB)]$) requirement compared to the nonobese subject for a given level of work. The increased metabolic work due to obesity is confirmed by a higher than expected $\dot{V}O_2$ during unloaded pedaling.

When the obese individual is relatively young, the increased oxygen cost for work caused by the large body mass is generally well tolerated (see Case 76, Chapter 10). In contrast, the normal deteriorating effects of aging on ventilatory capacity, combined with the extra ventilatory cost of moving a large body to perform work, results in a reduced breathing reserve. The breathing reserve can be further reduced because of ventilatory restriction imposed by the increased abdominal pressure, which resists diaphragmatic descent, and the reduced chest wall compliance. In addition to the ventilatory restriction, the cardiac output demand is increased to support the increased O_2 required to perform work. Thus, the cardiac reserve for exercise may be relatively low in the obese subject. Although the *AT* (when expressed as a percentage of predicted peak $\dot{V}O_2$) is normal, the obese subject's O_2 cost of walking may be too great to perform comfortably as compared to a nonobese subject.

Early Cardiovascular or Lung Disease (Branch Points 2.1-R and 2.3)

In early mild cardiovascular or lung disease, the disorder may not be severe enough to cause the peak $\dot{V}O_2$ to be less than predicted, because the predicted value is based on a relatively sedentary population. Specific physiological variables may become abnormal, however, depending on the site of the defect in the metabolic-cardiovascular-ventilatory coupling. For example, a patient may have a recently developed mild cardiovascular or pulmonary abnormality but still have a peak $\dot{V}O_2$ value that falls within the normal range. It may be difficult to document such a developing abnormality except by sequential studies demonstrating a decreasing peak $\dot{V}O_2$ or *AT* over time. The most common important diagnosis that should be identified or excluded in the middle-aged and elderly patient is ischemic heart disease. Also, to be excluded are subtle abnormalities in gas exchange that might suggest pulmonary vascular disease that limits the ability to recruit lung capillary bed in response to exercise. Thus, the most important measures during maximal effort exercise are the ECG and arterial blood gas values, along with analysis of gas exchange.

If the arterial blood gas values during exercise are normal (2.3-L), early heart disease, particularly coronary artery disease, may be present. ECG evidence of myocardial ischemia at peak $\dot{V}O_2$, along with gas exchange measurements that relate the increase in $\dot{V}O_2$ and $\dot{V}CO_2$ to the increase in work rate, may suggest the diagnosis of coronary artery disease. This will be indicated by an abrupt decrease in the rate of $\dot{V}O_2$ increase despite a sustained increase in work rate. This finding, with a low and nonincreasing O_2 pulse during increasing work rate, suggests myocardial dyskinesis, such as that found during exercise in patients with developing coronary artery disease. These changes, associated with an increase in O_2 pulse immediately at the start of recovery and ECG evidence of myocardial ischemia, support the diagnosis of coronary artery disease (2.3-L) (see Case 16, Chapter 10).

Abnormal changes in VD/VT, $P(a - ET)CO_2$, and $P(A - a)O_2$ as work rate is increased to the subject's maximum are the most sensitive markers of lung disease. Normal values essentially rule out mild or developing pulmonary vascular, lung parenchymal, or airway diseases because these measurements are almost always abnormal in those conditions (2.3-R). Resting pulmonary function tests, such as vital capacity, forced expiratory volume in one second (FEV_1), forced expiratory volume in one second/forced vital capacity (FEV_1/FVC), and diffusing capacity of the lung for carbon monoxide (DLCO), may be confirmatory. Sequential studies are very helpful for evidence of progression.

LOW PEAK OXYGEN UPTAKE WITH NORMAL ANAEROBIC THRESHOLD (FLOWCHART 3)

The breathing reserve provides a good first branch point for the differential diagnosis of disorders characterized by a low peak $\dot{V}O_2$ and a normal *AT* (Branch Point 3.1, Fig. 8.3). Patients with a normal or high breathing reserve (3.1-R) include those making a poor effort, those who are limited by muscular and skeletal diseases, or those who develop myocardial ischemia at work rates above their predicted *AT*. On the other hand, a low breathing reserve in a patient with a normal *AT* (3.1-L) identifies patients limited by their lung mechanics, rather than O_2 transport.

Normal or High Breathing Reserve (Branch Point 3.1-R)

Poor Effort or Musculoskeletal Disorder (Branch Point 3.3-L)

Poor effort or a musculoskeletal disorder–limiting exercise should be considered if the exercise ECG is normal.

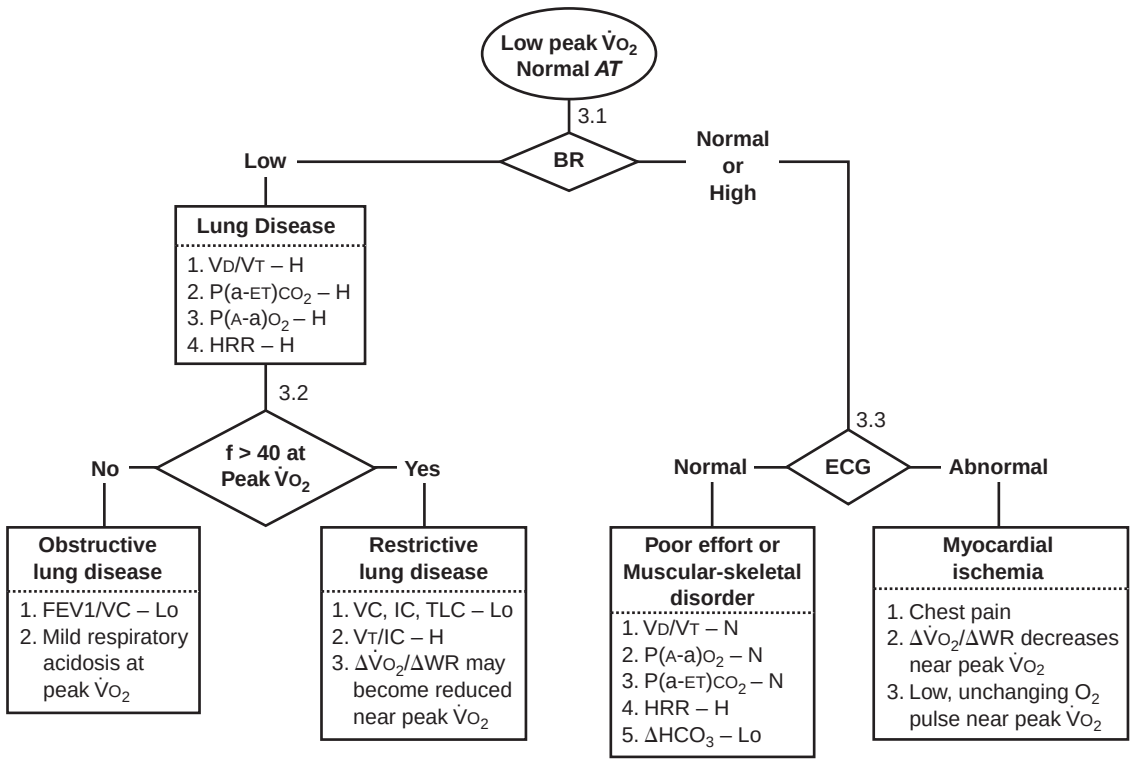

FIGURE 8.3. Flowchart 3 for conditions in which peak $\dot{V}O_2$ is low but the anaerobic threshold (*AT*) is normal. If the supporting measurements do not fit well, try a closely related branch point leading to a different diagnosis in which the supporting measurements fit better. Symbols and use of flowchart are as described in "Introduction to Flowcharts" and Figure 8.1.

Perhaps for secondary gain, the subject may make a poor effort and thereby have a low peak $\dot{V}O_2$ during exercise testing. Both the breathing reserve and heart rate reserve (HRR) will be high, indicating that the patient had not used the full potential of either the cardiovascular or the ventilatory systems. The absence of metabolic acidosis at the end of exercise is also evidence of poor effort. Normal exercise V_D/V_T, $P(A-a)O_2$, and $P(a-ET)CO_2$ confirm that the lungs and pulmonary circulation are functionally normal. These measurements demonstrate that the distribution of ventilation relative to perfusion is uniform, virtually ruling out primary lung or pulmonary vascular disease or significant chronic heart failure.

Simultaneous measurement of lactate and arterial blood for assessment of acid–base balance should confirm if an adequate effort was made during the exercise test. A lactic acidosis is the normal response to exercise when the test subject makes a reasonable maximal effort for an increasing work rate test. Thus, blood lactate should increase and $[HCO_3^-]$ decrease by at least 4 mmol/L at peak $\dot{V}O_2$. The rare exceptions are patients who have a defect in one of the skeletal muscle enzymes employed in the process of glycolysis (e.g., myophosphorylase, McArdle syndrome). Also, patients limited during exercise due to severe airflow obstruction or chest wall restriction may not be able to increase work rate sufficiently to develop a significant lactic acidosis during exercise. Certain patients with very severe heart failure and thus with very limited blood flow to exercising muscles might not be able to generate significantly high levels of lactate in their central circulation. These severe respiratory or heart disease patients would not be confused with a patient making a poor effort.

Optimal cardiovascular and pulmonary evaluation is impossible when arthritis or neuromuscular disease limits exercise. These patients have difficulty in performing enough exercise to stress the cardiovascular or respiratory systems sufficiently to bring out gas exchange abnormalities. However, a patient with exercise limitation may have both a musculoskeletal defect and a defect in the cardiovascular or respiratory system. Thus, it is important to distinguish if the exercise-induced lactic acidosis is driving ventilation beyond the subject's breathing ability, or breathing is so limited by impaired chest wall mechanics so that the CO_2 generated from aerobic metabolism cannot be normally regulated (see Case 61, Chapter 10).

Myocardial Ischemia (Branch Point 3.3-R)

Myocardial ischemia is induced by exercise in regions of the heart where the ability to increase myocardial blood (O_2) flow in response to the increased cardiac work is compromised. Thus, the ischemic part of the myocar-

dium is not able to generate sufficient ATP to sustain its contraction. This will be evident by a decreasing stroke volume, a slowing of the increase in $\dot{V}O_2$ relative to the increase in work rate, and an abnormally low and possibly decreasing O_2 pulse.

The ECG usually becomes abnormal if the myocardium becomes ischemic as the work rate is increased to the patient's symptom-limited maximum. For example, ECG abnormalities may be evident only at high work rates, beyond which the patient is tested. Also, some patients may not be tested during exercise because they do not experience chest pain. Whereas coronary artery disease is the most frequent cause of myocardial ischemia, it might also be seen with aortic stenosis or marked systemic hypertension without significant coronary artery disease (see Cases 22 and 70, Chapter 10).

At the start of an exercise test, a patient with ischemic heart disease would have a normal $\dot{V}O_2$/work rate of 10 mL/min/W. When the myocardium becomes ischemic as the myocardial work increases, $\dot{V}O_2$/work rate decreases (see Cases 18 and 22, Chapter 10). The most likely explanation for the slowing of the increase in $\dot{V}O_2$ is that the stroke volume decreases due to ischemia of part of the myocardium. Thus, the cardiac output fails to keep pace with the O_2 requirement despite a continuing increase in heart rate.

Low Breathing Reserve (Branch Point 3.1-L)

Low breathing reserve suggests lung disease in which respiratory mechanics limit minute ventilation. The breathing frequency may be a useful next branch point to determine if obstructive or restrictive lung disease dominates in patients with mixed obstructive and restrictive defects (Branch Point 3.2).

Obstructive Lung Diseases (Branch Point 3.2-L)

Although the peak $\dot{V}O_2$ achieved during incremental exercise testing is low in this disorder, the *AT* is often normal. The normal *AT* suggests that the patient does not have a primary problem with oxygen transport to the tissues at his or her peak work rate (see Case 49, Chapter 10). Rather, these patients may have a problem in regulating arterial H^+ (CO_2) during exercise. Also, due to ventilation–perfusion mismatching, they usually have abnormalities in PaO_2, V_D/V_T, $P(a-ET)CO_2$, and $P(A-a)O_2$ during exercise. Decreases in PaO_2 commonly occur in a single step at low work rates, with little further change as the work rate is increased (see Fig. 5.8). The absence of a further decrease in PaO_2 is probably because the increased lung perfusion during exercise goes predominantly to normal and high $\dot{V}A/\dot{Q}$ regions of the lungs rather than low $\dot{V}A/\dot{Q}$ regions. The breathing reserve is generally decreased, indicating a ventilatory limitation during exercise. In contrast to O_2 flow–limiting disorders, $\dot{V}O_2$ continues to increase linearly as the work rate is increased to the patient's peak $\dot{V}O_2$; thus, $\Delta\dot{V}O_2/\Delta WR$ continues to increase at the expected 10 mL/min/W as the peak $\dot{V}O_2$ is approached. The HRR is commonly increased because the cardiovascular response to the increasing work rate is not fully challenged due to the breathing limitation. Expiratory flow of the expiratory flow time plot frequently demonstrates an obstructive pattern (trapezoidal in appearance, with an early peak), as illustrated in Figure 4.15.

In patients with marked airflow obstruction, the *AT* measured by gas exchange usually is best determined by the V-slope method rather than methods that rely on the increase in ventilation, such as the ventilatory equivalent for O_2. Although CO_2 output will increase when HCO_3^- buffers lactic acid, the ventilatory response to the increased CO_2 load from buffering and the acidosis is often poor in patients with chronic obstructive pulmonary disease (COPD). Thus, the ventilatory equivalent for O_2 might not clearly increase at the *AT* (see Cases 47 and 49, Chapter 10). In these patients, the V-slope measurement is clearly the preferable method for determining the *AT*.

Restrictive Lung Diseases (Branch Point 3.2-R)

Patients with interstitial lung diseases (ILD) usually have a reduction in lung compliance, leading to restriction of lung expansion. The V_T increases to its maximum at a relatively low work rate. Thus, the ventilatory response to the increasing work rate is achieved primarily by increasing breathing frequency. The breathing frequency usually exceeds 40 breaths per minute at the end of exercise, with a V_T/IC close to 1. This is in contrast to the slower breathing rate adopted by patients with airflow limitation. The V_D/V_T and $P(a-ET)CO_2$ are increased in both restrictive and obstructive lung disorders as reflections of ventilation–perfusion mismatching.

Patients with ILD also have an O_2 flow problem (see Cases 39, 42, 55–57 in Chapter 10) as evidenced by a reduced *AT* and decreased $\Delta\dot{V}O_2/\Delta WR$. Reduced O_2 flow may be caused both by a falling arterial O_2 content, resulting in a narrowing of $C(a-\bar{v})O_2$, and increased pulmonary vascular resistance caused by destruction of pulmonary blood vessels by the fibrosing process. This limits the ability to increase cardiac output in response to exercise. ILD patients, therefore, have a reduced *AT* with a low peak $\dot{V}O_2$, similar to that of idiopathic pulmonary arterial disease, but with characteristic impaired lung mechanics. This diagnosis is analyzed in greater detail in Flowchart 4 (see Fig. 8.4).

LOW PEAK OXYGEN UPTAKE WITH LOW ANAEROBIC THRESHOLD (FLOWCHART 4)

The breathing reserve serves as a good first Branch Point (4.1) for the differential diagnosis of disorders having a low peak $\dot{V}O_2$ and low *AT*, as shown in Flowchart 4

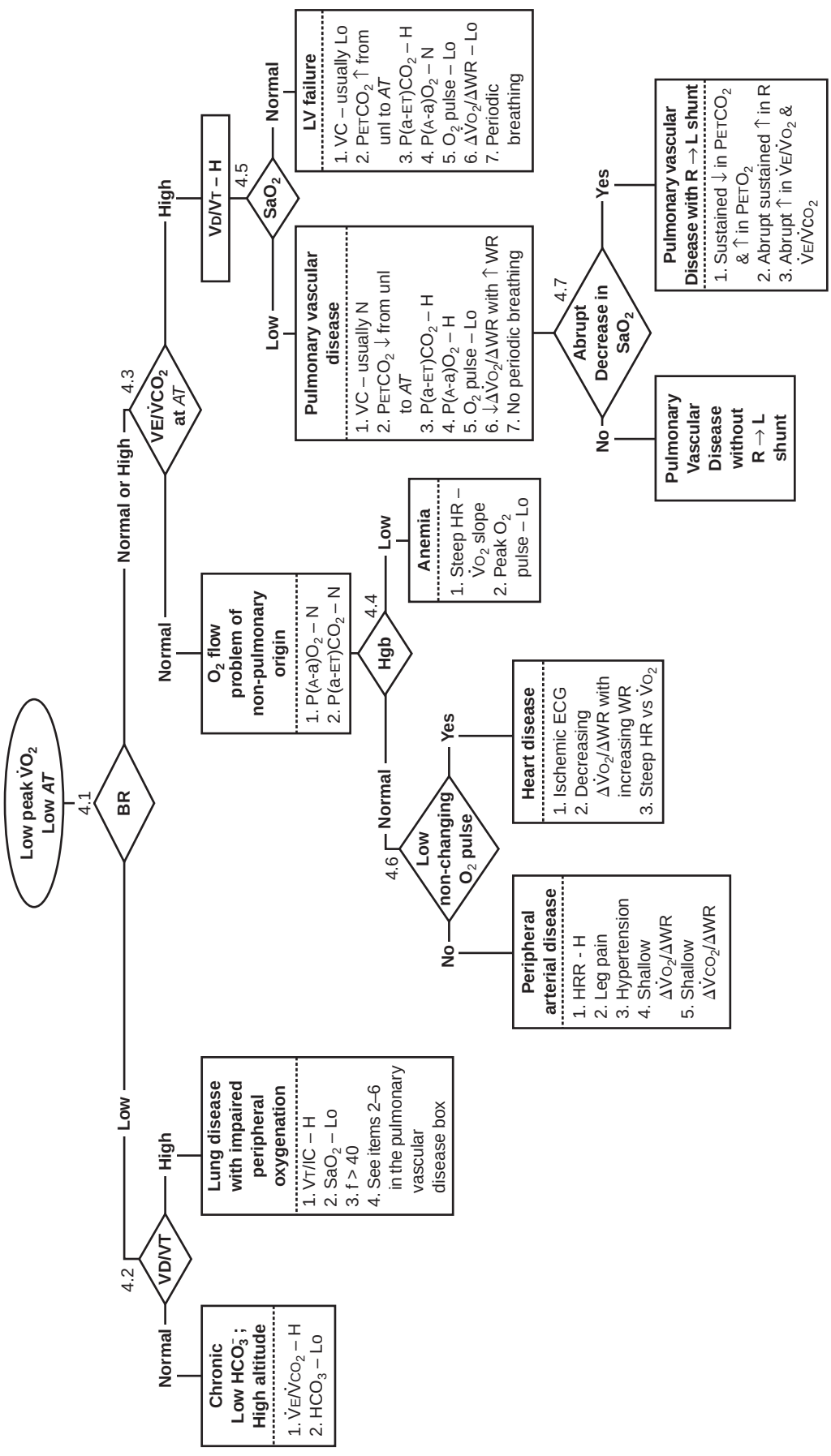

FIGURE 8.4. Flowchart 4 for conditions in which both peak $\dot{V}O_2$ and anaerobic threshold (*AT*) are reduced. If the supporting measurements do not fit well, try a closely related branch point leading to a different diagnosis in which the supporting measurements fit better. Symbols and use of flowchart are as described in "Introduction to Flowcharts" and Figure 8.1.

(Fig. 8.4), but further questions about pathophysiology need to be addressed to distinguish among the various conditions that cause a low *AT* as well as a low peak $\dot{V}O_2$. The V_D/V_T can be used as a second Branch Point (4.2) for the conditions that have a low breathing reserve; $\dot{V}E/\dot{V}CO_2$ at the *AT* or lowest $\dot{V}E/\dot{V}CO_2$ is a useful second Branch Point (4.3) for the conditions with a normal or high breathing reserve.

Normal or High Breathing Reserve (Branch Point 4.1-R)

Normal $\dot{V}E/\dot{V}CO_2$ at the Anaerobic Threshold (Branch Point 4.3-L)

If the breathing reserve is normal or high and the $\dot{V}E/\dot{V}CO_2$ at the *AT* is normal (4.3-L), then we must consider an O_2 flow problem of nonpulmonary vascular disease origin. This is because there is little physiological evidence of lung or pulmonary vascular disease or heart failure—that is, the breathing reserve and $\dot{V}E/\dot{V}CO_2$ at the *AT* are normal. Myocardial ischemia, low-grade cardiomyopathy, valvular heart disease, peripheral arterial disease, and anemia or hemoglobinopathy are diagnoses that should be considered because they can result in reduced O_2 flow during exercise, but with normal lung mechanics and uniform ventilation–perfusion relationships. Hemoglobin (Branch Point 4.4) and O_2 pulse (peak $\dot{V}O_2$/HR; Branch Point 4.6) help distinguish these diagnoses.

Anemia (Branch Point 4.4-R)

Because of the reduced O_2 carrying capacity of the blood, the *AT* and lactic acidosis occur at a lower than normal work rate. Anemia decreases the oxygen content of the arterial blood, leading to decreased maximal $C(a-\bar{v})O_2$. Thus, the maximal O_2 pulse is reduced. A higher cardiac output and heart rate are required to meet the tissue O_2 requirement. It should be noted that the arterial blood gas tensions and the V_D/V_T are normal in anemia, even at maximal exercise (see Case 51, Chapter 10).

Normal Hemoglobin (Branch Point 4.4-L)

Disorders with normal hemoglobin and impaired O_2 flow of nonpulmonary origin are chiefly heart disease and peripheral vascular disease.

Heart Disease (Branch Point 4.6-R)

Patients with primary heart disease (myocardial ischemia secondary to coronary artery disease, cardiomyopathy secondary to any cause, and valvular heart disease) usually have a low peak $\dot{V}O_2$ with a low *AT*. In these disorders, the rate of rise of $\dot{V}O_2$ is slow relative to the increase in work rate as the peak $\dot{V}O_2$ is approached (see Cases 12 to 20 in Chapter 10). However, the pattern of slowing differs according to diagnosis. The contrasting patterns of change are described in Figure 5.3 in Chapter 5. The heart rate often continues to increase as the work rate is increased, despite a slower increase of $\dot{V}O_2$, resulting in a steepening of the heart rate–$\dot{V}O_2$ relationship (Fig. 4.12) as the peak $\dot{V}O_2$ is approached. Also, the O_2 pulse reaches a constant value at subnormal values (see Fig. 4.8). Changes in the ECG consistent with myocardial ischemia during exercise, combined with concurrent failure of $\dot{V}O_2$ to increase normally, provide support for the diagnosis of exercise-induced myocardial ischemia (see Table 5.4).

In mild-to-moderate forms of heart failure, regardless of cause, acute metabolic acidosis occurs at relatively low levels of exercise. In more severe heart failure (New York Heart Association classes 3 to 4), V_D/V_T becomes elevated because of ventilation–perfusion mismatching. In such patients, the $\dot{V}E/\dot{V}CO_2$ is increased at the *AT*, and the flowchart leads to the right at Branch Point 4.3. Consequently, chronic stable advanced heart failure is accompanied by pulmonary vascular changes that must be distinguished from diseases in which the pulmonary circulation is a primary site of pathophysiology (see Tables 5.5 and 5.8).

Peripheral Arterial Disease (Branch Point 4.6-L)

In contrast to primary heart diseases, the HRR is generally high in patients in which peripheral arterial disease is predominant because the patient stops exercising due to leg pain before the heart is maximally stressed. Because of fixed stenosis of major conducting arteries, the normal decrease in peripheral vascular resistance in response to exercise cannot take place. Thus, systemic arterial hypertension develops beyond that expected with mild exercise. The increase in $\dot{V}O_2$ relative to the increase in work rate is reduced, resulting in a relatively shallow slope for the $\dot{V}O_2$–work rate relationship (low $\Delta\dot{V}O_2/\Delta WR$). In contrast to other cardiovascular disorders, the $\dot{V}CO_2$–work rate relationship is also abnormally shallow (low $\Delta\dot{V}CO_2/\Delta WR$). Finally, in the absence of concomitant lung disease, measurements of V_D/V_T, $P(a-ET)CO_2$, and $P(A-a)O_2$, which reflect the distribution of ventilation relative to perfusion, are normal (see Case 21, Chapter 10).

High $\dot{V}E/\dot{V}CO_2$ at the Anaerobic Threshold (Branch Point 4.3-R)

If the breathing reserve is normal or high (4.1-R) but the $\dot{V}E/\dot{V}CO_2$ at the *AT* or lowest value (see Fig. 4.21) is high (4.3-R), then the most likely disorder is either a disease originating in the pulmonary circulation or moderate to severe, but stable left ventricular failure. Both conditions manifest abnormalities in the pulmonary circulation, the former commonly, but not always, with and the latter without arterial hypoxemia.

Pulmonary Vascular Disease Originating in the Pulmonary Circulation (Branch Point 4.5-L)

Patients with pulmonary vascular disorders originating in the pulmonary circulation can often be distinguished

from pulmonary vascular changes that accompany left ventricular failure by a fall in arterial oxyhemoglobin saturation (Sa_{O_2}) at peak exercise in the former (Branch Point 4.5). Patients with primary pulmonary arterial occlusive diseases commonly develop arterial hypoxemia during exercise, although Sa_{O_2} might be normal at rest. If the physiological diagnosis is still unclear, the diagnostician should refer to changes in P_{ETCO_2} between unloaded exercise and *AT* (item 2 in the confirmatory boxes of the two diagnoses). In patients with a primary pulmonary vasculopathy, the P_{ETCO_2} usually decreases between unloaded exercise and the *AT*. In contrast, as in normal subjects, the P_{ETCO_2} increases between unloaded cycling and the *AT* in patients with left ventricular failure.[1]

Because of a reserve in the pulmonary vasculature available for recruitment during exercise in normal subjects, a pulmonary vasculopathy leading to pulmonary hypertension develops with a subtle onset. The initial symptoms occur only during exercise, usually with dyspnea. Pulmonary artery pressure may increase only during exercise. Primary disorders of the pulmonary circulation include pulmonary thromboembolic disease, primary pulmonary hypertension, and diseases that cause pulmonary vasculitis, such as various connective tissue diseases. Because of the loss of pulmonary capillary bed, the red cell residence time is shortened during exercise as cardiac output increases. This reduces the time for the P_{O_2} in the alveolus to equilibrate with that of the red cell during its shortened transit through the reduced pulmonary capillary bed. With sufficient right ventricular hypertrophy and reduced capillary bed, arterial oxygenation might decrease as work rate increases.

A decrease in Pa_{O_2} and Sa_{O_2} occurs abruptly during exercise if right atrial pressure exceeds the left atrial pressure. This causes desaturated venous right atrial blood to flow directly into the left atrium if there is a patent foramen ovale. The foramen ovale is potentially patent in about one-third of patients. This exercise-induced abnormality of lung gas exchange is usually seen at the start of exercise as a reduction in Pa_{O_2}, increased $P(A-a)O_2$, decreased Sa_{O_2} and a calculated increase in V_D/V_T.

If the pulmonary circulation, interposed between the right and left sides of the heart, does not dilate or recruit pulmonary blood vessels during exercise, the increased venous return that accompanies exercise cannot be readily transmitted to the left ventricle, and cardiac output cannot respond appropriately to the exercise stimulus. Because cardiac output does not increase normally, the increase in $\dot{V}O_2$ relative to increase in work rate progressively slows below the normal rate of increase of 10 mL/min/W. In addition to abnormal slowing in the rate of rise in $\dot{V}O_2$, the *AT* and peak $\dot{V}O_2$ are reduced. Because the increase in $\dot{V}O_2$ with work rate slows but heart rate continues to increase with work rate, heart rate increases steeply relative to $\dot{V}O_2$ and gets steeper as the peak $\dot{V}O_2$ is approached. Thus, the O_2 pulse fails to increase as the work rate is increased during exercise, and it is reduced at the maximum work rate.

Patients with all forms of pulmonary vascular disease have a high V_D/V_T and a positive value for $P(a-ET)CO_2$ during exercise, providing evidence of poor perfusion of ventilated air spaces. This is demonstrated noninvasively by an elevated $\dot{V}E/\dot{V}CO_2$ at *AT* or lowest $\dot{V}E/\dot{V}CO_2$, and abnormally steep $\dot{V}E$ versus $\dot{V}CO_2$ slope. Although these changes may be seen in patients with ILD, other measurements made during exercise distinguish these disorders. For instance, the breathing reserve is normal in patients with a primary pulmonary vasculopathy, whereas restrictive lung mechanics are present in patients with ILD. In addition, metabolic acidosis develops during exercise in patients with pulmonary vascular diseases, rather than the respiratory acidosis that commonly accompanies severe obstructive lung diseases in response to exercise (see Cases 47, 49, 75, and 77 in Chapter 10).

Primary lung diseases can cause major disturbances in function of the pulmonary circulation, which may become the dominant pathophysiological feature limiting exercise (see Cases 42, 48, and 50 in Chapter 10). In such instances, the abnormalities noted in the "Pulmonary Vascular Disease" diagnostic box of Flowchart 4 (see Fig. 8.4) become evident during exercise testing. Limitations in exercise caused by failure to recruit pulmonary circulation during exercise cannot be reliably predicted from resting measurements (see Chapters 5 and 9).

Pulmonary Vascular Disease with a Right-to-Left Shunt, or Cyanotic Congenital Heart Disease (Branch Point 4.7-R)

Patients with pulmonary vascular disease who open a potentially patent foramen ovale or who have congenital heart disease with a right-to-left shunt may demonstrate marked reductions in Pa_{O_2} during air and O_2 breathing in response to exercise (see Case 56, Chapter 10). The V_D/V_T, $P(a-ET)CO_2$, and $P(A-a)O_2$ values also become exceptionally abnormal, and become more abnormal as the work rate is increased, depending on the size of the right-to-left shunt. Patients with these disorders can be distinguished from those with other pulmonary vascular diseases by an abrupt and sustained decrease in P_{ETCO_2} and increase in P_{ETO_2}, sustained increases in R, $\dot{V}E/\dot{V}O_2$, and $\dot{V}E/\dot{V}CO_2$, and a decrease in arterial O_2 saturation as soon as exercise begins. O_2 pulse is low because of the reduced $C(a-\bar{v})O_2$ resulting from arterial hypoxemia. $\Delta\dot{V}O_2/\Delta WR$ is usually reduced because $\dot{V}O_2$ fails to increase appropriately as desaturated blood bypasses the lungs. Also, $\dot{V}E/\dot{V}O_2$ increases because $\dot{V}E$ increases disproportionally to $\dot{V}O_2$ in order to regulate arterial $[H^+]$ in compensation for the venous H^+ and CO_2 bypassing the lungs and flowing directly into the left side of the heart.

Repeating the exercise test while the patient breathes 100% O_2 is particularly helpful in distinguishing a right-to-left shunt from other causes of arterial hypoxemia.

When breathing 100% O_2, the arterial Pa_{O_2} will be in the range of 550 to 650 mm Hg at rest and at all levels of exercise in the absence of a right-to-left shunt. If a right-to-left shunt develops during exercise, Pa_{O_2} will fall precipitously even while breathing 100% O_2. It can be calculated that the arterial Pa_{O_2} will decrease by approximately 100 mm Hg for each 3% to 5% of the venous return that shunts from right to left while breathing 100% O_2 until Pa_{O_2} falls to about 150 mm Hg. This linear decrease in Pa_{O_2} is due to the reduction of physically dissolved O_2 in the arterial blood caused by the shunt. With a very large right-to-left shunt resulting in a Pa_{O_2} less than 150 mm Hg while breathing 100% O_2, the fall in Pa_{O_2} relative to the amount of shunt becomes nonlinear because of both reduced dissolved O_2 and oxyhemoglobin concentration.

Pulmonary Gas Exchanges Changes Secondary to Moderate to Severe Left Ventricular Failure (Branch Point 4.5-R)

Patients with moderate-to-severe left ventricular failure have an increased V_D/V_T and $P(a-ET)CO_2$, but without hypoxemia (normal Sa_{O_2}) at peak $\dot{V}_{O_2}$ (see Chapter 5). This increase in V_D/V_T and $P(a-ET)CO_2$ without hypoxemia indicate that ventilation–perfusion relationships are mismatched with high-$\dot{V}_A/\dot{Q}$ lung units, but without low-$\dot{V}_A/\dot{Q}$ lung units. This disparity between the abnormality in V_D/V_T and increase in $P(a-ET)CO_2$ (due to decrease in $P_{ET}CO_2$, not increase in Pa_{CO_2}), without a decrease in Sa_{O_2} and increase in $P(A-a)O_2$, is presumably accounted for by the slow pulmonary blood flow in left ventricular heart failure. The slow pulmonary blood flow of left ventricular failure allows adequate time for alveolar P_{O_2} to come into diffusion equilibrium with the red cell P_{O_2}, in contrast to the situation seen in primary pulmonary vascular occlusive diseases. The normal Pa_{O_2} and $P(A-a)O_2$ values at peak $\dot{V}_{O_2}$ distinguish left ventricular failure from pulmonary vascular disease originating in the pulmonary circulation. Because of the increase in V_D/V_T, the slope of $\dot{V}_E$ versus $\dot{V}CO_2$ (panel 6 of nine-panel graphical array, Figure 4.32) is abnormally steep in left ventricular failure, as it is in primary pulmonary vascular disease. These increases in V_D/V_T and slope of $\dot{V}_E$ versus $\dot{V}CO_2$ may not be present in mild left ventricular failure.

Low Breathing Reserve (Branch Point 4.1-L)

In the category of patients with a low peak $\dot{V}_{O_2}$ and low *AT* accompanied by a low breathing reserve and a high V_D/V_T (4.2-R), the most likely disorder is a primary lung disease such as pulmonary fibrosis (restrictive lung disease) or COPD in a sedentary patient. In contrast, a low breathing reserve with a normal V_D/V_T can be caused by diseases associated with a chronic metabolic acidosis with hyperventilation or a normal person adapted to high altitude (4.2-L). The following sections describe the pathophysiology that characterizes each of these disorders.

Lung Disease with Impaired Peripheral Oxygenation (Branch Point 4.2-R)

In certain pulmonary patients, the *AT* and peak $\dot{V}_{O_2}$ are reduced. Moreover, $\Delta\dot{V}_{O_2}/\Delta WR$ may be reduced as work rate is increased. These are usually patients with severe ILD or COPD in whom the pulmonary circulation is markedly impaired (see Table 5.11). Oxyhemoglobin desaturation may, but not necessarily, contribute to the impairment in O_2 flow to the exercising muscles. Commonly, the reduced $\Delta\dot{V}_{O_2}/\Delta WR$ is accompanied by a gradual reduction in the rate of increase in $\dot{V}_{O_2}$ as work rate is increased. The physiological explanation for this finding is that patients with ILD have a significant loss of pulmonary capillary bed caused by the disease process (see Chapter 5). Thus, if the pulmonary capillary bed is already maximally recruited at rest, pulmonary blood flow can increase to satisfy the increase in O_2 required for exercise only if pulmonary artery pressure increases. However, the degree of right ventricular hypertrophy may be insufficient to increase pulmonary blood flow (cardiac output) enough to support the O_2 required by the exercising muscle. Because the dominant pathophysiology in patients with ILD usually resides in the pulmonary circulation, the abnormalities described in the "Pulmonary Vascular Disease" box of Flowchart 4 (see Fig. 8.4) also apply to lung diseases with an O_2 transport problem (see Cases 42 and 56, Chapter 10).

Low Pa_{CO_2} Set Point (Branch Point 4.2-L)

There are several situations in which people have chronically low plasma HCO_3^-. To achieve normal pH, they will attempt to compensate by choosing a low Pa_{CO_2} set point, thereby requiring a higher than normal minute ventilation. These situations include people who get ill at high altitude domiciles, or sea-level patients with chronic metabolic acidosis due to chronic renal failure, renal tubular acidosis, or poorly controlled diabetes mellitus with partially compensated metabolic acidosis, or patients taking acetazolamide (e.g., carbonic anhydrase inhibitor for glaucoma). In these patients, a higher alveolar and minute ventilation are needed to clear the increased metabolic CO_2 at a lower Pa_{CO_2}, generated during exercise (see Fig. 2.43). Similarly, the Pa_{CO_2} set point is low in people who reside at high altitude. The low Pa_{CO_2} results in higher ventilatory equivalents for O_2 and CO_2 (increased ventilatory drive), thereby decreasing the breathing reserve at maximum exercise. Because of the high ventilatory requirement, these patients may experience exertional dyspnea before reaching their predicted sea-level peak $\dot{V}_{O_2}$ and *AT*. Exertional dyspnea is especially likely to occur in patients with a low Pa_{CO_2} when accompanied by lung or

heart disease, anemia, or obesity. A low P_aCO_2 set point is easily identified from arterial blood gas and pH measurements at rest.

LOW PEAK OXYGEN UPTAKE WITH ANAEROBIC THRESHOLD NOT DETERMINED (FLOWCHART 5)

The importance of the *AT* in deciding the cause of exercise limitation is demonstrated in the previous flowcharts. Since the development of the V-slope method to determine the *AT*, the effect of breathing irregularities or failure to increase ventilation relative to $\dot{V}O_2$ increase is no longer a problem. The V-slope detected *AT* is the $\dot{V}O_2$ at which $\dot{V}CO_2$ starts to increase faster than $\dot{V}O_2$ during a progressively increasing work rate test. This is the same relationship as cardiac output × $C(v - a)CO_2$ versus cardiac output × $C(a - v)O_2$. An *AT* is part of everyone's exercise physiology. However, in some patients, the *AT* may not be determined by gas exchange because the rate of increase in work rate was too slow relative to the subject's work capacity. Alternatively, the interpreter may feel that the *AT* is unreliable because of breathing irregularities. Failure to identify an *AT* may also result from the patient stopping exercise before the *AT* is reached, either volitionally or due to breathing restriction secondary to abnormal lung mechanics. The interpreter then knows that the *AT* is greater than the peak $\dot{V}O_2$ of the study.

An alternative strategy to using the *AT* as the second major branch point in the decision-making process (Flowchart 1) is described in Flowchart 5 (Fig. 8.5). Given a reduced peak $\dot{V}O_2$, tests that detect mismatching of ventilation to perfusion make it possible to distinguish disorders associated with inefficiency of lung gas exchange from disorders associated with normal lung function and pulmonary circulation. Thus, Branch Point 5.1 uses arterial blood gas and pulmonary gas exchange measurements to identify the presence of mismatching of ventilation to perfusion. Diseases associated with abnormal ventilation–perfusion relationships include restrictive lung diseases, obstructive lung diseases, pulmonary vascular diseases, and left ventricular failure. Patients with acute coronary syndromes without chronic heart failure, mild left ventricular failure, anemia, peripheral arterial disease, and poor effort have normal ventilation–perfusion relationships.

The simplest and cheapest way to detect the presence of ventilation–perfusion mismatching reliably is the measurement of V_D/V_T, $P(a - ET)CO_2$, and $P(A - a)O_2$ during exercise, using direct arterial blood gas and simultaneous gas exchange measurements. In the absence of arterial blood, an alternative is to approximate P_aCO_2 from venous blood drawn from a superficial vein of a warmed hand or from arterialized capillary blood from an ear lobe. From these measurements, V_D/V_T and $P(a - ET)CO_2$ can be calculated.

But strong suspicion of ventilation–perfusion mismatch can be obtained noninvasively from measurement of $\dot{V}E/\dot{V}CO_2$ at the ventilatory compensation point (VCP) or its lowest values during exercise (see Chapters 4, 7, and 9). These measurements have a very narrow normal range and are characteristically abnormal in conditions in which ventilation–perfusion relationships become nonuniform. Therefore, if these noninvasive (surrogate) variables for V_D/V_T are abnormal, we can say that $\dot{V}A/\dot{Q}$ is nonuniform with reasonable but not absolute confidence. Acute hyperventilation will artificially elevate the $\dot{V}E/\dot{V}CO_2$ and reduce $P_{ET}CO_2$. However, if the respiratory exchange ratio (R) is not abnormally elevated (below 1.0), then these surrogate markers of uneven ventilation relative to perfusion are most likely reliable. As shown in Flowchart 5 (Fig. 8.5), if V_D/V_T, $P(a - ET)CO_2$, and $P(A - a)O_2$ (or the surrogate measurements for $\dot{V}A/\dot{Q}$ mismatch just mentioned) are normal (5.1-L), we examine the HRR (5.2); if V_D/V_T, $P(a - ET)CO_2$, and $P(A - a)O_2$ values (or $\dot{V}E/\dot{V}CO_2$ and $P_{ET}CO_2$ at the VCP) are abnormal (5.1-R), we examine the breathing reserve (5.3). The possible diagnoses at each of these branch points separate into two major groups depending on whether the HRR is normal or high or the breathing reserve is normal or low.

Normal V_D/V_T, $P(a - ET)CO_2$, and $P(A - a)O_2$ (Branch Point 5.1-L)

Heart disease, anemia, poor effort, and peripheral arterial disease are all associated with a low peak $\dot{V}O_2$ but have normal indices of gas exchange efficiency [V_D/V_T, $P(a - ET)CO_2$, and $P(A - a)O_2$]. The HRR allows this group to be further subdivided into those with a normal HRR (Branch Point 5.2-L; heart disease or anemia) or a high HRR (Branch Point 5.2-R; poor effort, peripheral arterial disease, and heart failure with chronotropic incompetence).

Anemia can be distinguished from the heart disorders with a low peak $\dot{V}O_2$, uniform $\dot{V}A/\dot{Q}$, and normal HRR (Branch Point 5.2-L) by a low hemoglobin concentration (Branch Point 5.4). Ischemic, valvular, cardiomyopathic, or noncyanotic congenital heart diseases are usually characterized by a greater rise in heart rate and lesser rise in $\dot{V}O_2$ than expected for the work rate performed.

Poor effort, peripheral arterial disease, and mild-to-moderate chronic heart failure with chronotropic incompetence are associated with a low peak $\dot{V}O_2$, uniform $\dot{V}A/\dot{Q}$, and high HRR (Branch Point 5.2-R). The $\Delta\dot{V}O_2/\Delta WR$ (Branch Point 5.5) is a useful branch point to distinguish poor effort (normal $\Delta\dot{V}O_2/\Delta WR$) from peripheral arterial disease and chronic heart failure with chronotropic incompetence (low $\Delta\dot{V}O_2/\Delta WR$). Poor effort can be confirmed by other measurements, including a high

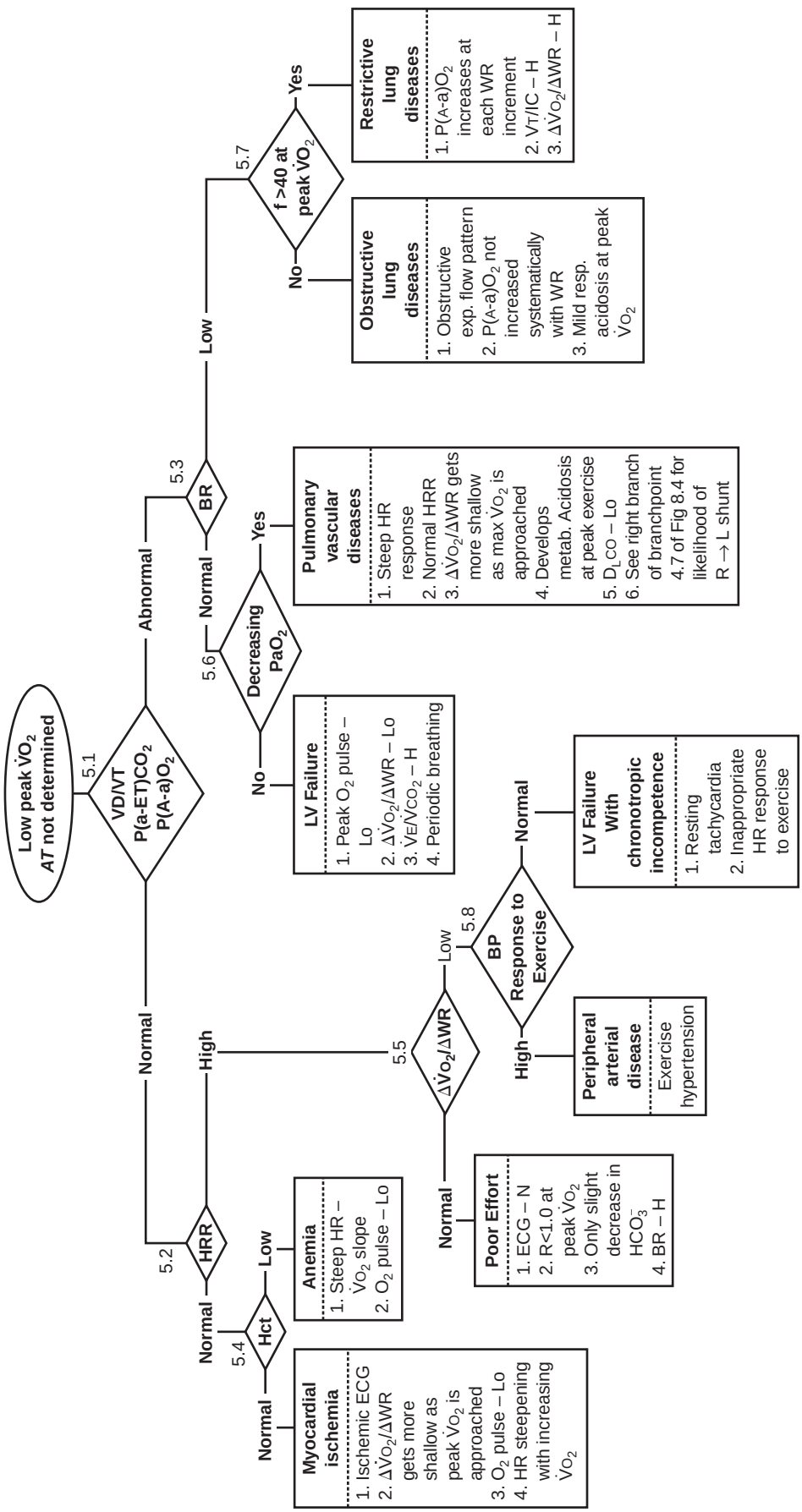

FIGURE 8.5. Flowchart 5 for conditions in which peak $\dot{V}O_2$ is low but the anaerobic threshold (*AT*) has not been measured or cannot be reliably determined. If the supporting measurements do not fit well, try a closely related branch point leading to a different diagnosis in which the supporting measurements fit better. Symbols and use of flowchart are as described in "Introduction to Flowcharts" and Figure 8.1.

breathing reserve, failure to develop a significant metabolic acidosis at end of exercise, an R less than 1.0 at the peak $\dot{V}O_2$, a normal ECG, and possibly a very irregular breathing pattern.

Patients with peripheral arterial disease and those with left ventricular failure with chronotropic incompetence usually have a low $\Delta\dot{V}O_2/\Delta WR$ and $\Delta\dot{V}CO_2/\Delta WR$ (Branch Point 5.5-R). Further distinguishing these diagnoses is a pronounced systolic hypertension in response to exercise in the former, but normal or low systolic pressure response in the latter (Branch Point 5.8).

Abnormal V_D/V_T, $P(a-ET)CO_2$, and $P(A-a)O_2$ (Branch Point 5.1-R)

Pulmonary vascular diseases, chronic left ventricular heart failure, and obstructive and restrictive lung diseases are associated with a low peak $\dot{V}O_2$ and abnormal indices of gas exchange efficiency (nonuniform $\dot{V}A/\dot{Q}$). The breathing reserve (Branch Point 5.3) subdivides these patients into those with a normal breathing reserve (heart failure and pulmonary vascular diseases) and those with a low breathing reserve (obstructive and restrictive lung diseases).

The two disorders with a low peak $\dot{V}O_2$ and nonuniform $\dot{V}A/\dot{Q}$ but a normal breathing reserve (Branch Point 5.3-L) can usually be distinguished by the PaO_2 or arterial oxyhemoglobin (O_2Hb) saturation in response to exercise (Branch Point 5.6). The patient with pulmonary vascular disease commonly has a normal PaO_2 or arterial O_2Hb saturation at rest that decreases progressively as the work rate increases (Branch Point 5.6-R). If pulmonary vascular disease is accompanied by a right-to-left shunt, such as in cyanotic congenital heart disease or the opening of an unsealed foramen ovale with exercise, then the decrement in PaO_2 at the start of exercise will be marked. Item 6 in the diagnostic box for pulmonary vascular diseases (see Fig. 8.5) describes simple measurements that can support the development of a right-to-left shunt during exercise. The patient with moderately severe left ventricular failure will have a normal PaO_2 and arterial O_2Hb saturation, even at maximum exercise, although V_D/V_T will be elevated as with primary pulmonary vasculopathies (Branch Point 5.6-L).

Both obstructive and restrictive lung diseases have a low peak $\dot{V}O_2$, nonuniform $\dot{V}A/\dot{Q}$, and low breathing reserve (Branch Point 5.3-R), but can generally be distinguished by the breathing frequency and the measurements listed in the respective diagnostic boxes for obstructive and restrictive lung diseases. A breathing frequency higher than 40 at the patient's peak $\dot{V}O_2$ is commonly associated with restrictive lung disease (Branch Point 5.7-R), whereas a breathing frequency less than 40 at the peak $\dot{V}O_2$ is characteristic of the patient with obstructive lung disease (Branch Point 5.7-L). Although the distinction between obstructive and restrictive lung disease is generally evident from standard pulmonary function measurements, the question addressed by exercise testing is whether or not the resting pulmonary function abnormalities account for the patient's exercise intolerance or some associated pathophysiology (e.g., heart disease).

SUMMARY

To determine the likely pathophysiological causes of exercise limitation, we found that a logical approach can be developed and displayed in five flowcharts. Each flowchart starts with a question regarding whether the peak $\dot{V}O_2$ is normal or abnormal. Other physiological measurements relating *AT*, breathing reserve, heart rate and $\dot{V}O_2$, ventilation–perfusion relationship, and $\Delta\dot{V}O_2/\Delta$ work rate are then used to define the pathophysiological sites in the gas transport coupling of muscle metabolism to gas exchange at the airway. The identified pathophysiology can be used to establish the likely clinical diagnosis.

Flowchart 1 separates four major categories of patients. Flowchart 2 addresses the cause of exercise limitation in patients with a normal peak $\dot{V}O_2$. Flowchart 3 considers the diagnosis in patients with a reduced peak $\dot{V}O_2$ but with a normal *AT*. Flowchart 4 considers the diagnoses in patients with a reduced peak $\dot{V}O_2$ and reduced *AT*. Finally, Flowchart 1 addresses the diagnoses of the patient with a reduced peak $\dot{V}O_2$ but with the *AT* not determined. These flowcharts usually enable the examiner to make a specific organ-related physiological diagnosis. The flowcharts are designed as guides to an orderly decision-making process. The final judgment must be made by the examiner.

REFERENCE

1. Hansen JE, Ulubay G, Chow BF, et al. Mixed-expired and end-tidal CO_2 distinguish between ventilation and perfusion defects during exercise testing in patients with lung and heart diseases. *Chest*. 2007;132:977–983.

CHAPTER

9

Clinical Applications of Cardiopulmonary Exercise Testing

The increasing number of applications for which cardiopulmonary exercise testing (CPET) is currently employed attests to the growing recognition of its importance in medicine. This chapter describes current applications of CPET. In some instances, these applications are well established, as described in a number of reviews.[7,9,10,12,44,72,111,129] In others, the applications are inadequately recognized and appreciated. The applications of CPET are of great value in patient care and have the potential to reduce health care costs by streamlining diagnosis and facilitating treatment decisions.

DIFFERENTIAL DIAGNOSIS OF DISORDERS CAUSING EXERCISE INTOLERANCE

The physician is sometimes at a loss to determine and understand the pathophysiological mechanism(s) causing exercise intolerance; therefore, the disease that accounts for the patient's symptom(s)—usually those of fatigue, dyspnea, or pain—goes undiagnosed. Different defects in the coupling of external (airway) to cellular respiration affect gas exchange in different ways (see Fig. 5.1), with the gas exchange responses to CPET differing according to the defect. Thus, the pattern of gas exchange at the airway can be used to identify pathophysiology and also to support or refute the correctness of a specific clinical diagnosis. With an appropriate display of gas exchange data obtained during exercise testing, it is possible to determine the functional status of the cardiovascular and ventilatory systems.

There are also certain diagnoses for which CPET is a unique diagnostic tool. That is, the diagnosis can be inferred from the gas exchange responses to exercise, but cannot be made very easily with other diagnostic modalities. These include exercise intolerance due to silent myocardial ischemia; chronic heart failure due to diastolic dysfunction; primary pulmonary vascular occlusive disease without overt pulmonary hypertension; the development of a right-to-left shunt during exercise; pulmonary vascular disease limiting exercise in chronic obstructive pulmonary disease (COPD); disorders of skeletal muscle that impair muscle bioenergetic function; and psychogenic dyspnea and behavioral causes of exercise intolerance, such as anxiety or secondary gain. In addition, there is no faster or more inexpensive way of confirming a normal bioenergetic, cardiovascular and ventilatory physiological state than CPET. It is capable of confirming, in one test, if the cardiac output responses to specific exercise work rates, the state of ventilation–perfusion matching, breathing pattern, and the ventilatory responses to exercise are normal, without the need of multiple and more expensive studies.

We find that a graphical display of CPET data showing the essential physiological responses to be easier to interpret than a tabular display. It is particularly useful to assemble these data into nine strategically positioned panels containing 16 graphs on a single page (see Fig. 4.32). These graphs enable the examiner to assess, systematically, the cardiovascular, ventilatory, ventilation–perfusion, and metabolic responses to exercise. Armed with this information, the cause of exercise intolerance can usually be determined with a high degree of certainty.

A major reason why the patterns of gas exchange data for different diseases can be recognized on the nine-panel graphical display is that gas exchange responses are very uniform in healthy subjects. For example, the increase in $\dot{V}O_2$ as related to work rate is normally approximately 10 mL/min/W with relatively small standard deviation (±0.7; see Chapter 2). Because the heart rate normally increases linearly with $\dot{V}O_2$, the heart rate–$\dot{V}O_2$ and the O_2 pulse responses are highly predictable. Also, the relative uniformity of P_aCO_2 and V_D/V_T values in normal subjects and the tight regulation of arterial H^+ concentration (see Chapters 2, 3, and 7) show that the normal ventilatory response to exercise is closely coupled to $\dot{V}CO_2$ below the anaerobic threshold (*AT*), with small variation (see Table 7.6).

Chapter 8 discusses how a diagnosis can be reached using a deductive physiological reasoning strategy. After determining that the peak $\dot{V}O_2$ is reduced, a systematic series of questions are asked about other physiological measurements. In the following section, specific panels from the nine-panel graphical display (Fig. 4.32) are used to contrast the responses seen in several common disorders. By contrasting the response patterns of key physiological responses to exercise in eight different diseases with the normal responses, we believe it will become clearer how the patterns of the CPET variables in response to exercise help in the differential diagnosis of disorders limiting exercise. However, it must be stressed that a diagnosis is not made by examining one panel or variable alone. Making a specific diagnosis usually depends on specific abnormalities in certain panels and normal responses in others.

PATHOPHYSIOLOGY OF COMMON DISORDERS

Oxygen Uptake, Carbon Dioxide Output, and Work Rate as Related to Time

The basic requirement to sustain muscular exercise is an increase in cellular respiration for regeneration of the adenosine triphosphate (ATP) to fuel the muscular contractions. To support the increase in cellular respiration, O_2 and CO_2 transport between the cells and the environment must match the rate of cellular respiration (except for transient lags allowed by the capacitances in energy stores and the transport system). The increases in O_2 and CO_2 transport are functions of the peripheral circulation, heart, pulmonary circulation, blood, lungs, and respiratory muscles. Any defect in this interactive system could result in failure of the exercising muscles to take up

and use the O_2 needed for aerobic regeneration of ATP. On the nine-panel graphical display (see Fig. 4.32 and Chapter 10), $\dot{V}O_2$, $\dot{V}CO_2$, and work rate (WR) are plotted against time during rest, exercise, and early recovery in panel 1 (upper left). The diagonal is work rate plotted on a scale that is one-tenth of the $\dot{V}O_2$ scale; therefore, a parallel increase in $\dot{V}O_2$ to the work rate increase indicates that $\Delta\dot{V}O_2/\Delta WR$ is equal to 10 mL/min/W (Figs. 4.32 and 9.1), which is normal. A shallower slope indicates an under utilization of O_2 and anaerobiosis, usually due to a cardiovascular abnormality, such as shown in Figure 5.3.

Figure 9.1 contrasts the characteristic findings of $\dot{V}O_2$, $\dot{V}CO_2$, and WR plotted against time for a normal patient (Fig. 9.1A) contrasted with eight other patients with different pathophysiologies (Fig. 9.1B–I). The age, gender, and predicted $\dot{V}O_2$ for each patient are shown in their respective panels. Figure 9.1A (Case 1 in Chapter 10) shows the responses of a normal 55-year-old man. This is the only subject shown in Figure 9.1 with a normal peak $\dot{V}O_2$, $\dot{V}CO_2$ response, and $\Delta\dot{V}O_2/\Delta WR$. $\dot{V}O_2$ increases linearly and parallel to work rate with a slope of 10 mL/min/W, the predicted normal slope.

Figure 9.1B (Case 18 in Chapter 10) shows $\dot{V}O_2$, $\dot{V}CO_2$, and work rate plotted against time for a 47-year-old man who developed ST segment changes on the electrocardiogram (ECG) after $\dot{V}O_2$ stopped increasing normally during a progressively increasing work rate test of 25 W per minute. The failure for $\dot{V}O_2$ to increase at 10 mL/min/W, starting abruptly at a specific work rate (about 150 W in this patient), despite a normal increase at lower work rates, is common in coronary artery disease (CAD). We hypothesize that the abrupt reduction in the $\dot{V}O_2$ -work rate slope is due to developing myocardial dyskinesis due to critical myocardial ischemia. The latter reduces stroke volume, reflected in a low, flat O_2 pulse (Fig. 9.3B), impairing the heart's ability to increase cardiac output and O_2 transport normally.[18,64]

Figure 9.1C (Case 21 in Chapter 10) displays data for a 65-year-old male cigarette smoker with diabetes and peripheral arterial disease. Both $\dot{V}O_2$ and $\dot{V}CO_2$ increase linearly—but more slowly than normal—from the lowest work rate, as might be predicted for someone with a fixed stenosis of the conducting arteries to exercising extremities. Unique to dominant peripheral arterial disease is the simultaneous shallow increase in both $\dot{V}CO_2$ and $\dot{V}O_2$. This contrasts with cardiovascular impairments involving the heart or pulmonary circulation in which the steepening of $\dot{V}CO_2$ persists, despite a shallower $\dot{V}O_2$. In these conditions, the decrease in CO_2 from aerobic metabolism is offset by CO_2 production from bicarbonate buffering of lactic acid.

The study shown in Figure 9.1D (Case 14 in Chapter 10) is of a 57-year-old woman with dilated cardiomyopathy. She had a significantly reduced peak $\dot{V}O_2$ and a low *AT* reflected by a relatively high CO_2 output at low work rates. Indices of ventilation-perfusion mismatching in chronic left ventricular failure is reflected in Figure 9.6D.

The study shown in Figure 9.1E (Case 40 in Chapter 10) is of a 54-year old male with vasculitis that primarily affected his pulmonary circulation. The rate of rise in $\dot{V}O_2$ decreases progressively as the peak $\dot{V}O_2$ is approached. Thus, the average $\Delta\dot{V}O_2/\Delta WR$ is quite low despite a steep $\Delta\dot{V}CO_2/\Delta WR$ slope. The abnormal gas exchange efficiency accompanying this pulmonary vascular disease is addressed in Figures 9.5 and 9.6.

The high O_2 cost of exercise during treadmill walking in an obese subject can be seen in Figure 9.1F (Case 76 in Chapter 10), which demonstrates the large increase in $\dot{V}O_2$ following the onset of walking at zero grade at 3 miles per hour. Because the actual work rate performed on a treadmill is very difficult to determine, $\Delta\dot{V}O_2/\Delta WR$ cannot be readily calculated.

The data in Figure 9.1G (Case 46 in Chapter 10) are those of a 50-year-old man with COPD. The $\Delta\dot{V}O_2/\Delta WR$ is normal, but the peak $\dot{V}O_2$ is reduced. Abnormal ventilatory mechanics and reduced gas exchange efficiency contribute to his exercise limitation, as shown in Figures 9.4G and 9.6G, respectively.

Exercise data from a 29-year-old man with sarcoidosis resulting in severe pulmonary hypertension are shown in Figure 9.1H (Case 42 in Chapter 10). The very low peak $\dot{V}O_2$ and reduced $\Delta\dot{V}O_2/\Delta WR$ place him in the severely impaired category.

Finally, the study shown in Figure 9.1I (Case 56 in Chapter 10) is of a 20-year-old man with severe interstitial pulmonary fibrosis (IPF), but without pulmonary hypertension. His failure to increase $\dot{V}O_2$ despite increasing work rate reflects his inability to increase pulmonary blood flow and the maximizing of $C(a-\bar{v})O_2$ at a very low work rate. This finding represents very severe disease and a loss of ability to sustain even mild exercise. The lack of pulmonary hypertension in this patient is due to failure of the right ventricle to hypertrophy and does not connote the absence of severe loss of pulmonary vascular bed. The high $\dot{V}CO_2$ relative to $\dot{V}O_2$ reflects the substantial lactic acidosis that the patient developed during this short exercise test. With the exception of very severe cardiovascular disease, the respiratory gas exchange ratio (R) increases at the start of recovery (Fig. 9.9). However, in both patients in Figure 9.1H and I, as is characteristic of severe cardiovascular diseases, the R decreased. Apparently because of the circulatory limitation, the recovery of the O_2 debt was slow while $\dot{V}CO_2$ recovery progressed. This resulted in a decreasing, rather than a normal increasing, $\dot{V}CO_2/\dot{V}O_2$ at recovery onset.

Heart Rate and Carbon Dioxide Output as a Function of Oxygen Uptake

Panel 3 of the nine-panel graphical array (Fig. 4.32) shows heart rate and $\dot{V}CO_2$ as functions of $\dot{V}O_2$. These relationships

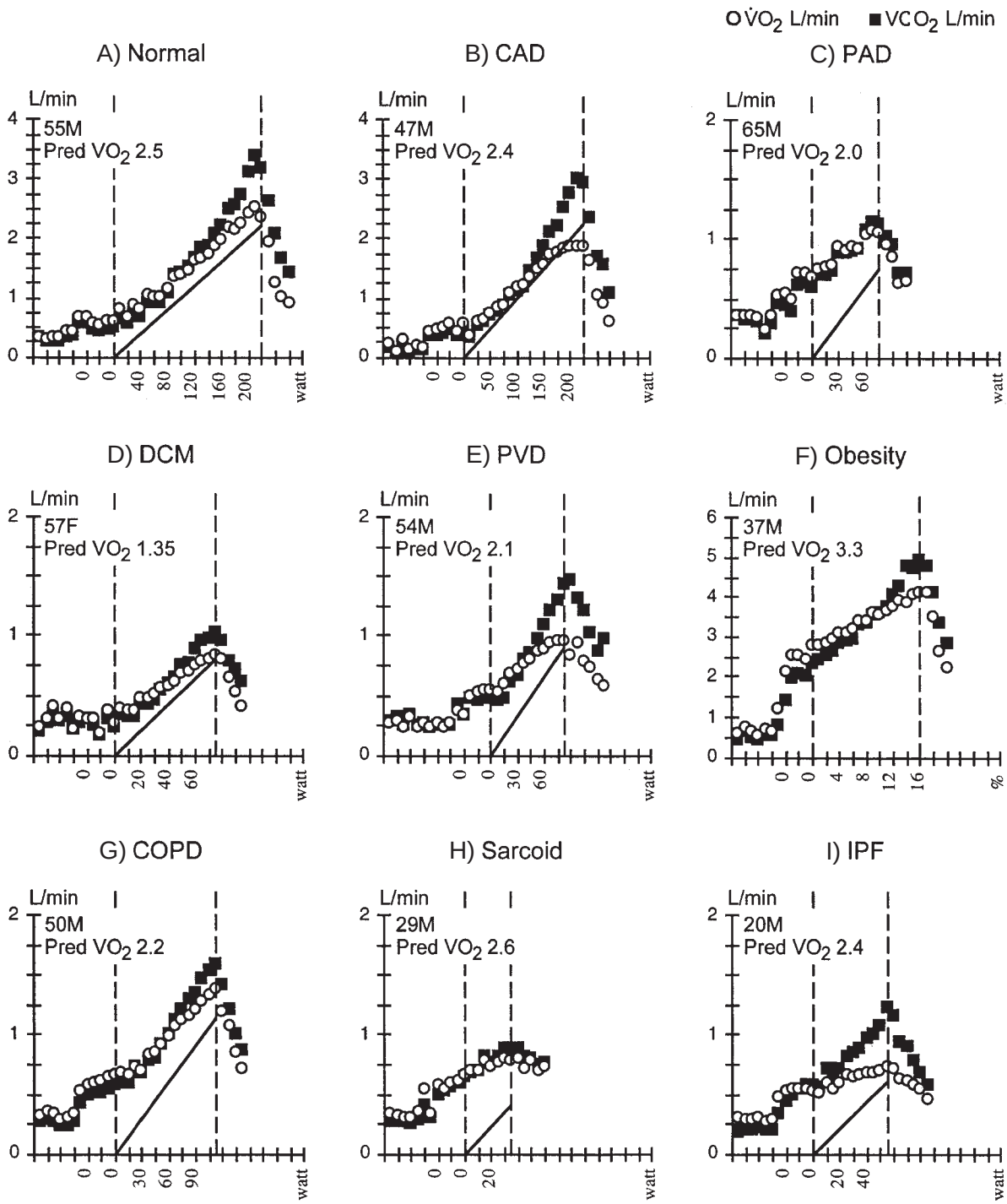

FIGURE 9.1. Plot of $\dot{V}O_2$ and $\dot{V}CO_2$ (STPD) as a function of work rate (watts) and time (1 minute between tick marks on x-axis) for patients with normal exercise performance **(A)**, coronary artery disease (CAD) **(B)**, peripheral arterial disease (PAD) **(C)**, dilated cardiomyopathy (DCM) **(D)**, pulmonary vascular disease (PVD) **(E)**, obesity (abscissa is % treadmill grade) **(F)**, chronic obstructive pulmonary disease (COPD) **(G)**, sarcoidosis **(H)**, and interstitial pulmonary fibrosis (IPF) **(I)**. The data to the left of the first *0* are from the rest period. Zero work rate is unloaded cycling. The period of increasing work rate starts at the *left vertical dashed line* and ends at the *right vertical dashed line.* The *diagonal line* between the *vertical dashed lines* is the normal rate of rise for $\dot{V}O_2$ against work rate with a slope of 10 mL/min/W. The predicted peak $\dot{V}O_2$ is shown in the upper left of each panel. Just above the predicted peak $\dot{V}O_2$ are the age and gender of the patient. Further history and data can be found for each patient in Chapter 10. The Chapter 10 case number for the patients shown in panels A, B, C, D, E, F, G, H, and I are 1, 18, 21, 14, 40, 76, 46, 42, and 56, respectively, for this and Figures 9.2–9.9.

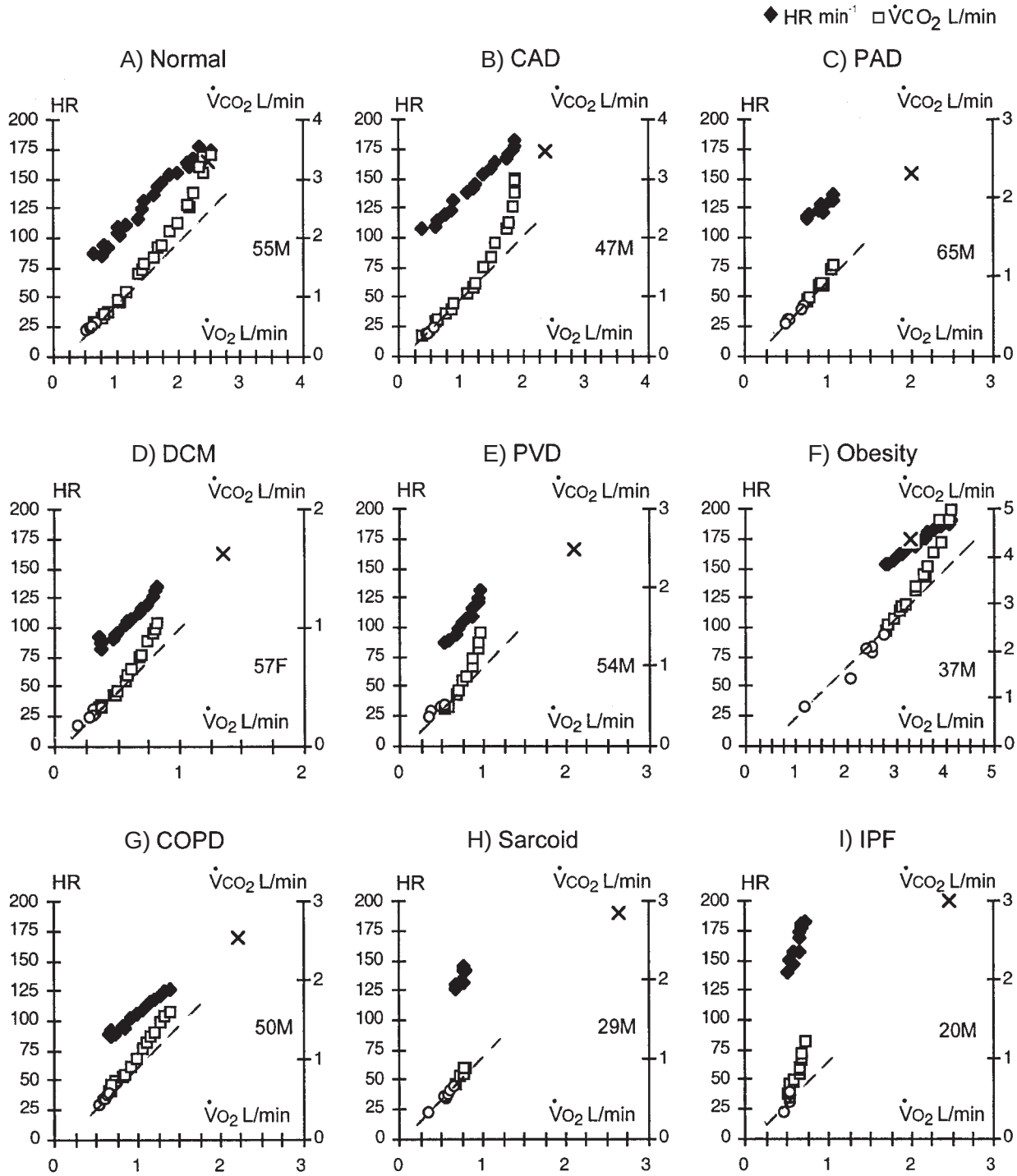

FIGURE 9.2. Heart rate and $\dot{V}CO_2$ plotted as functions of $\dot{V}O_2$ for the same nine patients shown in Figure 9.1. The *diagonal dashed line* has a slope of 1. The anaerobic threshold (*AT*) is read as the $\dot{V}O_2$ at which $\dot{V}CO_2$ starts increasing at a slope greater than 1.

are shown in Figure 9.2 for the same nine patients depicted in Figure 9.1. Heart rate normally increases linearly with $\dot{V}O_2$ to the predicted maximum values for both variables, as indicated by the *X* in the figure and illustrated in Figure 9.2A (Case 1 in Chapter 10). The heart rate–$\dot{V}O_2$ slope is steeper than normal and often becomes nonlinear in the patients with cardiovascular diseases (Fig. 9.2B, D), including those in which the diseases affect the pulmonary circulation, such as pulmonary vasculitis (Fig. 9.2E), sarcoidosis (Fig. 9.2H), and IPF (Fig. 9.2I).

$\dot{V}CO_2$ normally increases as a function of $\dot{V}O_2$ with a slope of approximately 1, or slightly less until the *AT* is reached (Fig. 9.2A). Above that point, $\dot{V}CO_2$ increases more steeply than $\dot{V}O_2$ in all of the patients except in the patient with peripheral arterial disease (Fig. 9.2C). In this patient, CO_2 is presumably trapped in the muscle

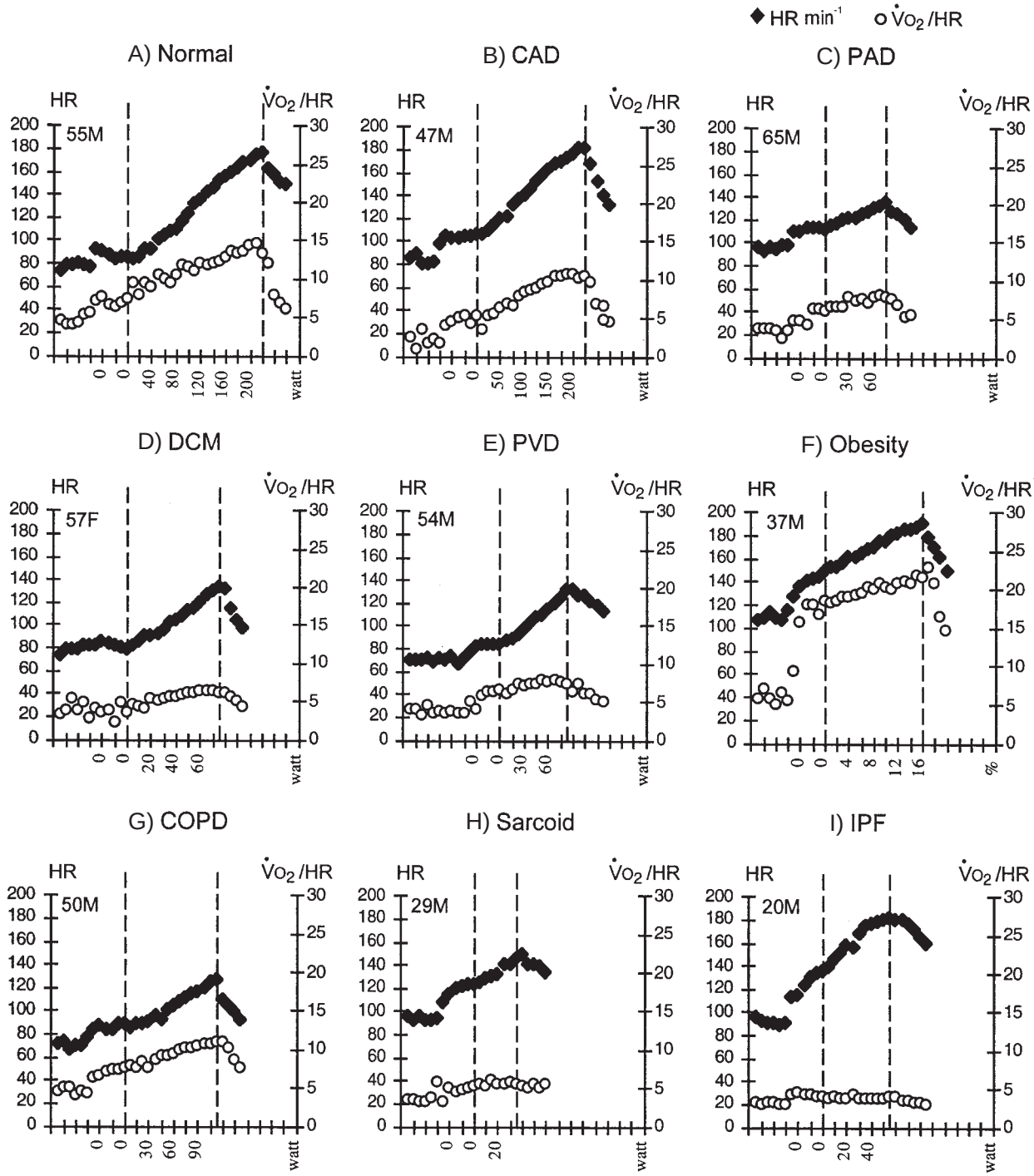

FIGURE 9.3. Heart rate (HR) and O_2 pulse ($\dot{V}O_2$/HR) plotted as functions of work rate (watts) and time (1 minute between tick marks on *x*-axis) for the same nine patients shown in Figure 9.1. The period of increasing work rate starts at the *left vertical dashed line* and ends at the *right vertical dashed line*.

because of the abnormally low blood flow coming from the ischemic lower limbs. In the patient with CAD (Fig. 9.2B), the obese patient (Fig. 9.2F), and the patient with COPD (Fig. 9.2G), the *AT* is normal. In the patient with heart failure (Fig. 9.2D) and the three other patients (vasculitis, Fig. 9.2E; sarcoidosis, Fig. 9.2H; and IPF, Fig. 9.2I), the *AT* is significantly below the 95% confidence limit for normal.

Heart Rate and Oxygen Pulse as a Function of Time

Panel 2 of the nine-panel graphic array (Fig. 4.32) shows the heart rate and O_2 pulse plotted against time and work rate. Figure 9.3 shows panel 2 for the same nine patients included in Figure 9.1. Heart rate normally increases abruptly at the start of unloaded cycling and

then increases approximately linearly with work rate to the predicted maximal heart rate (Fig. 9.3A). Deviation from the normal heart rate response is seen in patients with chronotropic incompetence (Fig. 9.3D) or when the patient is stopped in the performance of exercise because of noncardiac or nonpulmonary vascular disease problems. The latter is exemplified by the patients with peripheral arterial disease (Fig. 9.3C) and COPD (Fig. 9.3G).

The O_2 pulse, the product of stroke volume and arteriovenous O_2 difference (also graphed in panel 2), normally increases but with a gradually decreasing rate of rise to the predicted normal value (Fig. 9.3A). However, O_2 pulse fails to increase normally in patients with CAD in whom myocardial ischemia reduces stroke volume and therefore exercise capacity (Fig. 9.3B). The O_2 pulse also fails to increase normally in heart failure (Fig. 9.3D), as well as in the three patients in whom the pulmonary circulation is seriously deranged (pulmonary vasculitis, sarcoidosis, and IPF). As shown in Figure 9.3E, H, and I, the value of peak O_2 pulse during exercise is abnormally low in these patients.

The O_2 pulse can also be discerned from the panels shown in Figure 9.2. The O_2 pulse is low when the extension of the slope of the heart rate–$\dot{V}O_2$ relationship projects to the left of the target *X* (e.g., Fig. 9.2B–E, H, and I).

Tidal Volume as a Function of Exercise Minute Ventilation

Tidal volume (V_T) is plotted as a function of $\dot{V}_E$ in panel 9 of the nine-panel graphical array (Fig. 4.32). Figure 9.4 shows panel 9 for the same nine patients illustrated in Figure 9.1. Tidal volume normally increases, preferentially, more than breathing frequency during low- and moderate-intensity exercise to account for the early increase in $\dot{V}_E$ in normal subjects (Fig. 9.4A). Above the *AT*, breathing frequency is the primary variable accounting for the increase in $\dot{V}_E$. At peak exercise, there is normally a breathing reserve of greater than 10 to 15 L/min, calculated as the difference between the maximal voluntary ventilation (MVV) and the peak exercise $\dot{V}_E$. The tidal volume may increase to the inspiratory capacity, but not above it.

Patients limited in their exercise tolerance by lung mechanics characteristically have a very small breathing reserve (<10 L/min) or none at all. Thus, despite only a moderate reduction in MVV, the patient with COPD commonly has no breathing reserve when ventilatory limited due to a combination of poor gas exchange efficiency and reduced ventilatory capacity (Fig. 9.4G). This is also true of the patient with IPF (Fig. 9.4I). Further, the patient with IPF has a tidal volume that reaches inspiratory capacity early in exercise, characteristic of restrictive lung disease. The breathing reserves in the other patients in Figure 9.4 are normal.

Exercise Minute Ventilation as a Function of Carbon Dioxide Output

$\dot{V}_E$ is plotted as a function of $\dot{V}CO_2$ in panel 6 of the nine-panel graphical array. Figure 9.5 shows panel 6 for the nine patients illustrated in Figure 9.1. $\dot{V}_E$ normally increases linearly with $\dot{V}CO_2$ with a slope of 23 to 28 (Table 7.6) in normal subjects up to the point where ventilatory compensation for the developing lactic acidosis starts (Fig. 9.5A). This slope is not increased in patients with CAD (Fig. 9.5B), peripheral arterial disease (Fig. 9.5C), and obesity (Fig. 9.5F). However, it is usually increased in patients with chronic heart failure (Fig. 9.5D),[33,48,69,81,141] pulmonary vasculitis (Fig. 9.5E), COPD (Fig. 9.5G), sarcoidosis (Fig. 9.5H), and IPF (Fig. 9.5I), as well as diseases associated with an increased V_D/V_T,[69,70,142,148] a reduced arterial PCO_2, or both. The slope of the linear component of the plot of $\dot{V}_E$ versus $\dot{V}CO_2$ is steeper the more extensive the disease.[48,69,137,144]

Ventilatory Equivalents for Oxygen and Carbon Dioxide versus Time

$\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ are plotted against time and work rate, in panel 6 of the nine-panel graphic array (Fig. 4.32). Figure 9.6 shows panel 4 for the nine patients illustrated in Figure 9.1. When V_D/V_T and $PaCO_2$ are normal, $\dot{V}_E/\dot{V}O_2$ decreases and reaches a nadir at the *AT* with a value approximately less than 28, and $\dot{V}_E/\dot{V}CO_2$ decreases to a nadir between the *AT* and ventilatory compensation point with a value approximately less than 32, as shown in Figure 9.6A. The nadir values of $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ are normal for patients with CAD (Fig. 9.6B), peripheral arterial disease (Fig. 9.6C), and obesity (Fig. 9.6F), but increased for patients with chronic heart failure (Fig. 9.6D), pulmonary vasculitis (Fig. 9.6E), COPD (Fig. 9.6G), sarcoidosis (Fig. 9.6H), and IPF (Fig. 9.6I), diseases associated with an increase in V_D/V_T. The more severe the disease or the lower the $PaCO_2$, the higher the values of $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$.

End-Tidal Oxygen and Carbon Dioxide Tensions versus Time

$PETO_2$ and $PETCO_2$—and, when available, PaO_2 and $PaCO_2$—are plotted against time and work rate, in panel 7 of the nine-panel graphical array (Fig. 4.32). Similarly, oxyhemoglobin saturation values determined by pulse oxymetry are plotted in panel 7, if arterial blood gas measurements are unavailable. Figure 9.7 shows panel 7 for the nine patients illustrated in Figure 9.1. Normally, $PETO_2$ and $PETCO_2$ track their arterial blood counterparts (Fig. 9.7A), with $PaCO_2$ higher than $PETCO_2$ at rest, but $PETCO_2$ becoming approximately 4 mm Hg higher than $PaCO_2$ during exercise (Fig. 9.7A). $PETCO_2$ increases with exercise to the *AT* to a value slightly above 40 mm Hg at sea-level altitudes when the pulmonary circulation is normal, such

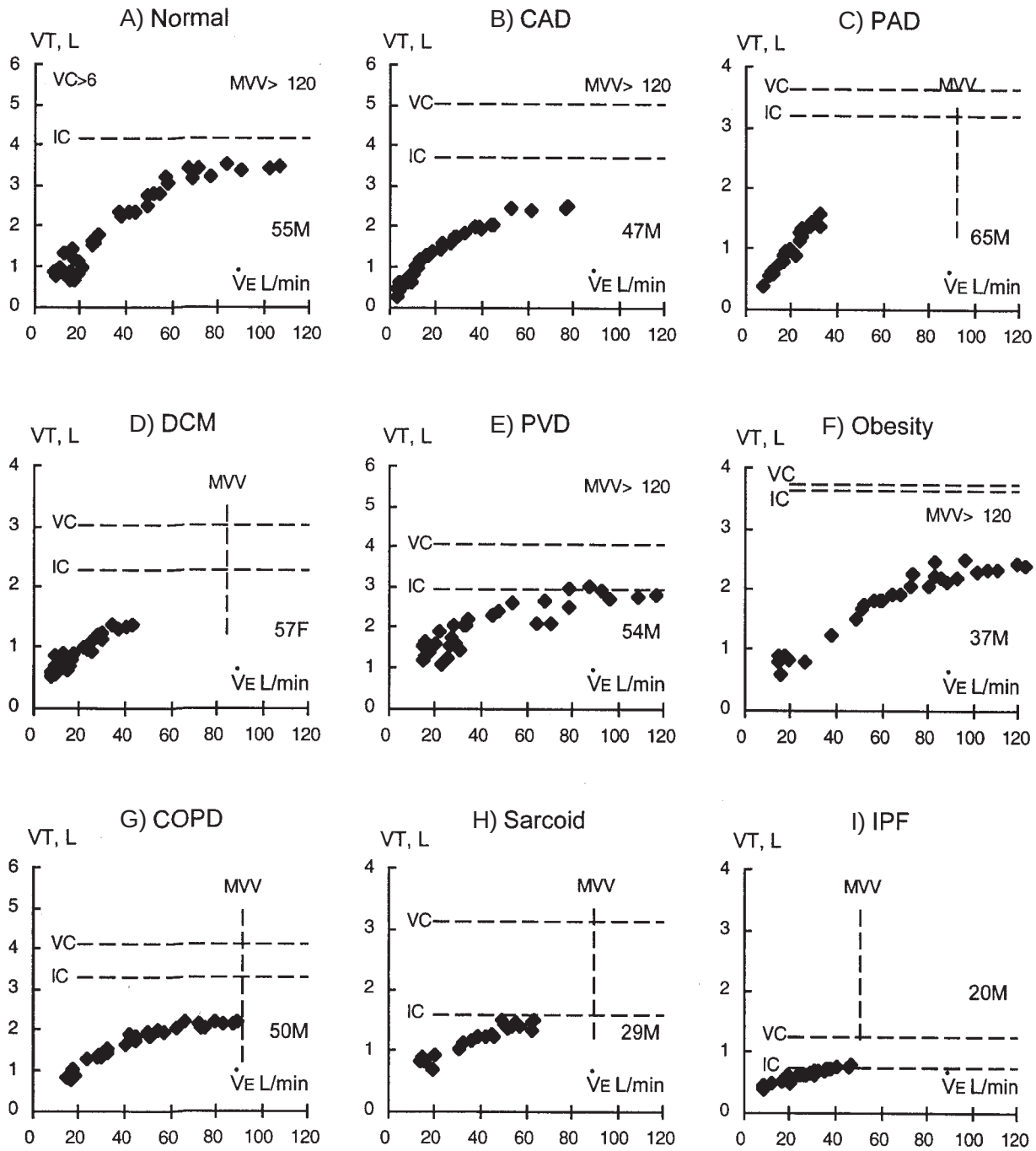

FIGURE 9.4. Exercise tidal volume plotted as a function of minute ventilation ($\dot{V}_E$) for the same nine patients shown in Figure 9.1. Also shown are the subject's maximal voluntary ventilation (MVV) on the abscissa (*vertical dashed line*) and the subject's resting inspiratory capacity (IC) and vital capacity (VC) on the ordinate (*horizontal dashed lines*) unless above scale.

as shown in the cases of the patients with CAD (Fig. 9.7B), peripheral arterial disease (Fig. 9.7C), and obesity (Fig. 9.7F). $P_{ET}O_2$ shows a reciprocal decrease to the *AT*.

The increase in $P_{ET}CO_2$ during exercise is greater than normal in severely obese patients because the mechanical restriction caused by the excessively heavy chest wall and abdomen prevents ventilation from keeping a precise pace with the increase in CO_2 production (Fig. 9.7F).

In severe heart failure (Fig. 9.7D), $P_{ET}CO_2$ is reduced because blood flow is slow relative to ventilation in regional lung units. At rest and low work rates, $P_{ET}CO_2$ might be quite variable in left ventricular failure because of the periodic breathing that these patients commonly develop (see Cases 14 and 74 in Chapter 10). This is reflected in panel 7 of the nine-panel plot as a regular oscillatory change in $P_{ET}CO_2$ and $P_{ET}O_2$ at rest and low work rates (Fig. 9.7D).

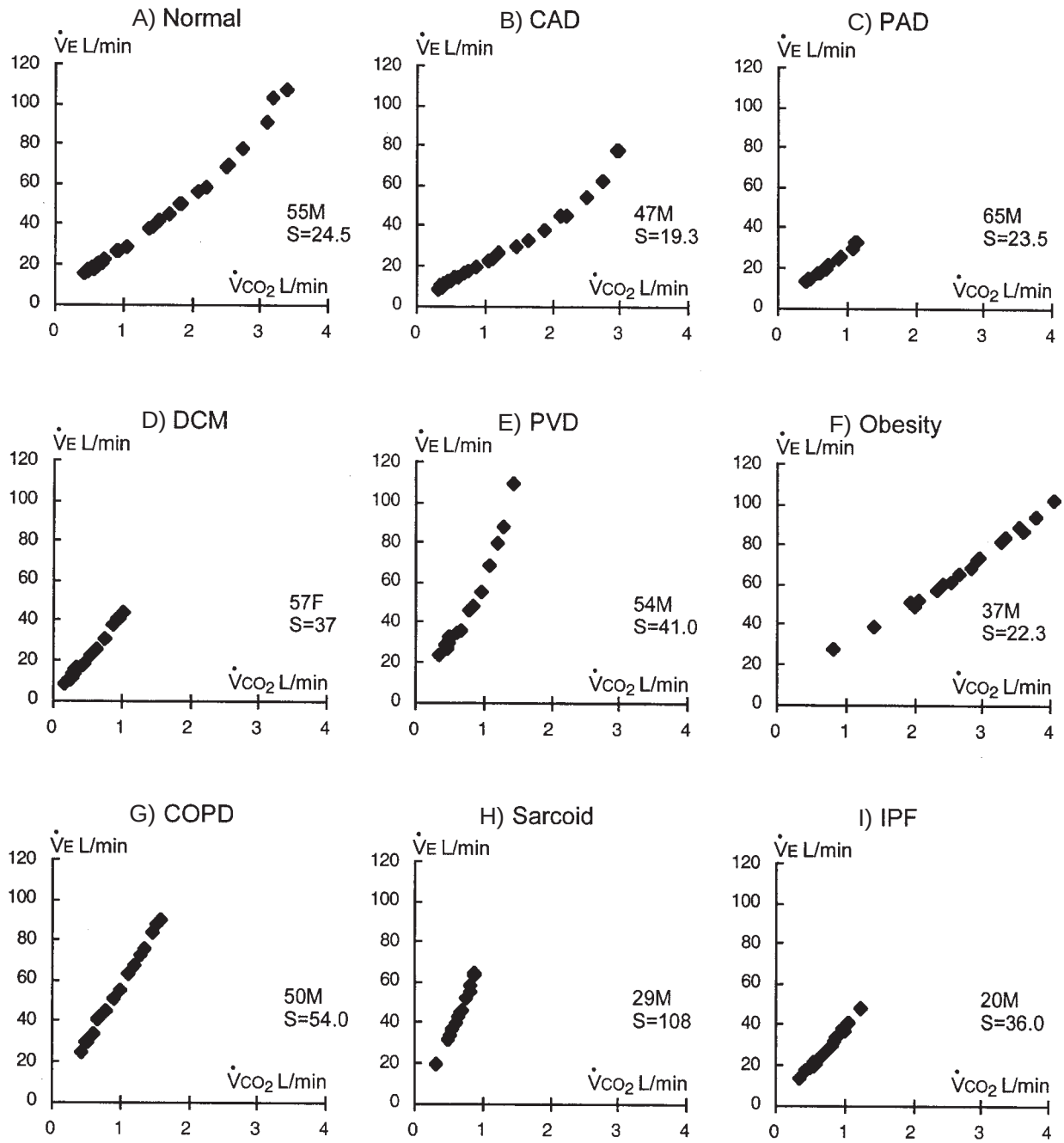

FIGURE 9.5. Exercise minute ventilation ($\dot{V}E$) plotted as a function of CO_2 output ($\dot{V}CO_2$) for the same nine patients shown in Figure 9.1. At lower right in each panel is the slope (S) of the linear component of the $\dot{V}E$ versus $\dot{V}CO_2$ relationship.

Consequently, at rest and low work rate exercise, two sets of values appear, as shown in Figure 9.7D.

P_{ETCO_2} is reduced in pulmonary vascular occlusive disease (Fig. 9.7E) because of lack of perfusion of ventilated lung. The underperfused acini function as dead space because they contain little CO_2 as compared with the ideal alveolar or arterial P_{CO_2}. Thus, the mixed end-tidal gas is relatively dilute in CO_2, and P_{ETCO_2} is less than P_{aCO_2}, in contrast to the pattern seen in normal subjects (Fig. 9.7A).

In patients with COPD, the P_{ETCO_2} is reduced relative to P_{aCO_2} because the high-$\dot{V}A/\dot{Q}$ lung units account for most of the subject's ventilation (Fig. 9.7G). If airway obstruction is quite severe, P_{ETCO_2} might increase in response to exercise.

Figure 9.7H shows a case of a young man with severe sarcoidosis. In this disorder, the pulmonary circulation may be greatly affected, reducing the size of the pulmonary vascular bed. Thus, P_{ETCO_2} is markedly reduced relative to P_{aCO_2} (Fig. 9.7H). P_{aO_2} might also

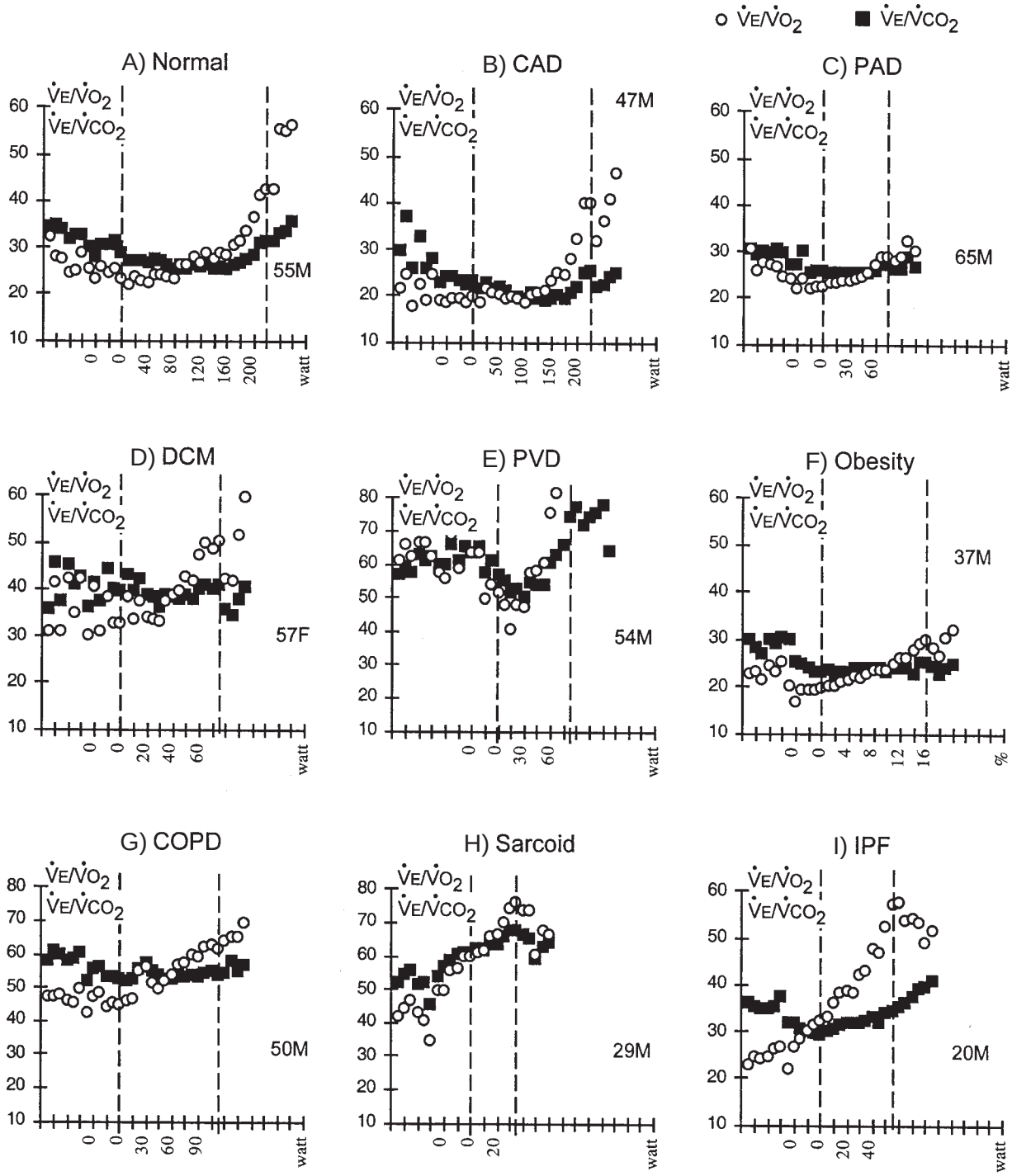

FIGURE 9.6. Plot of ventilatory equivalent for O_2 ($\dot{V}E/\dot{V}O_2$) (*open circles*) and CO_2 ($\dot{V}E/\dot{V}CO_2$) (*closed squares*) as functions of time (1 minute between tick marks on *x*-axis) and work rate, for the same nine patients shown in Figure 9.1. The period of increasing work rate starts at the *left vertical dashed line* and ends at the *right vertical dashed line*.

be markedly reduced, as in Figure 9.7H, particularly if the foramen ovale opens during exercise, shunting right atrial blood into the left atrium.[136] This commonly occurs at the start of exercise when the increase in venous return raises right atrial pressure. It is seen as an abrupt increase in $P_{ET}O_2$ and decrease in $P_{ET}CO_2$ with increase in R and $\dot{V}E/\dot{V}O_2$ at the start of exercise. As an example of the changes in $P_{ET}O_2$ and $P_{ET}CO_2$ with development of a right-to-left shunt at the start of exercise, see Case 36 in Chapter 10.

$P_{ET}CO_2$ decreases below $PaCO_2$ in idiopathic pulmonary fibrosis. Normally, $PaCO_2$ is regulated near normal if

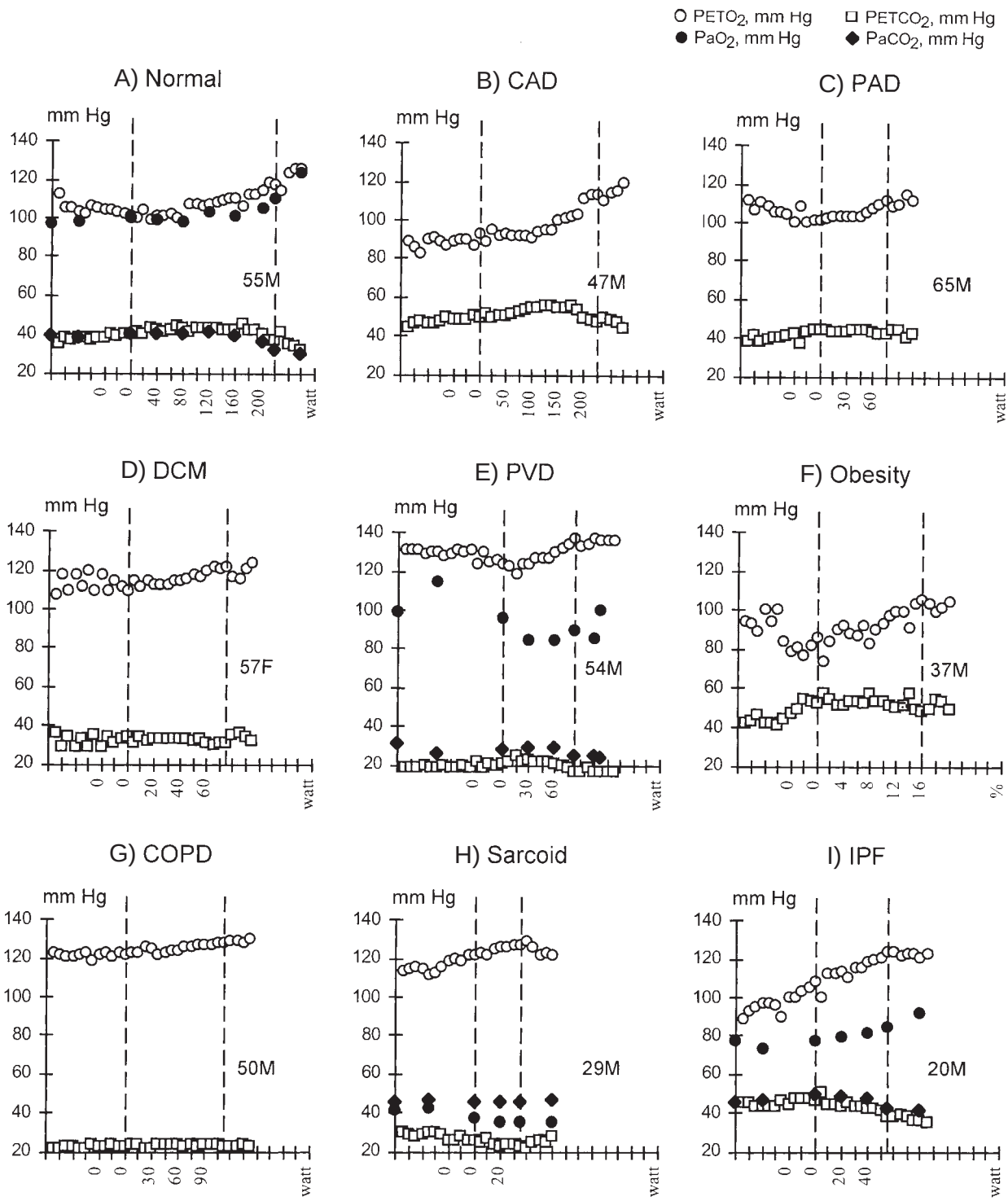

FIGURE 9.7. Plot of P_{ETO_2} and P_{ETCO_2}, and in four cases, the corresponding arterial values, as functions of time (1 minute between tick marks on *x*-axis) and work rate, for the same nine patients shown in Figure 9.1. The period of increasing work rate starts at the *left vertical dashed line* and ends at the *right vertical dashed line*.

the lung mechanics are not too severely affected. However, if lung mechanics are severely impaired, hypercapnia may take place during exercise (Fig. 9.7I).

In subjects with good chemosensitivity, $\dot{V}_E$ increases nonlinearly at the *AT*, causing P_{ETO_2} to increase without a decrease in P_{ETCO_2} (isocapnic buffering; Fig. 9.7A–F, H, I). Thus, panel 7 can be used as a method for detecting the *AT*. However, it is not as reliable a method as the V-slope method because the former depends on good chemoreceptor sensitivity. This is not a requirement of the lat-

ter method. Compare the *AT* determined from Figure 9.7 with that of Figure 9.2.

Minute Ventilation and Systolic Blood Pressure as a Function of Time

$\dot{V}_E$ and systolic blood pressure are plotted as a function of time and work rate, in panel 5 of the nine-panel graphical array (Fig. 4.32). Figure 9.8 shows panel 5 for the nine patients illustrated in Figure 9.1. $\dot{V}_E$ normally increases linearly with work rate and time in normal subjects up to the point where ventilatory compensation for the developing lactic acidosis starts (Fig. 9.8A). The slope of $\dot{V}_E$ versus increasing work rate and time remains relatively linear in patients whose ventilation is relatively restricted, such as in obesity

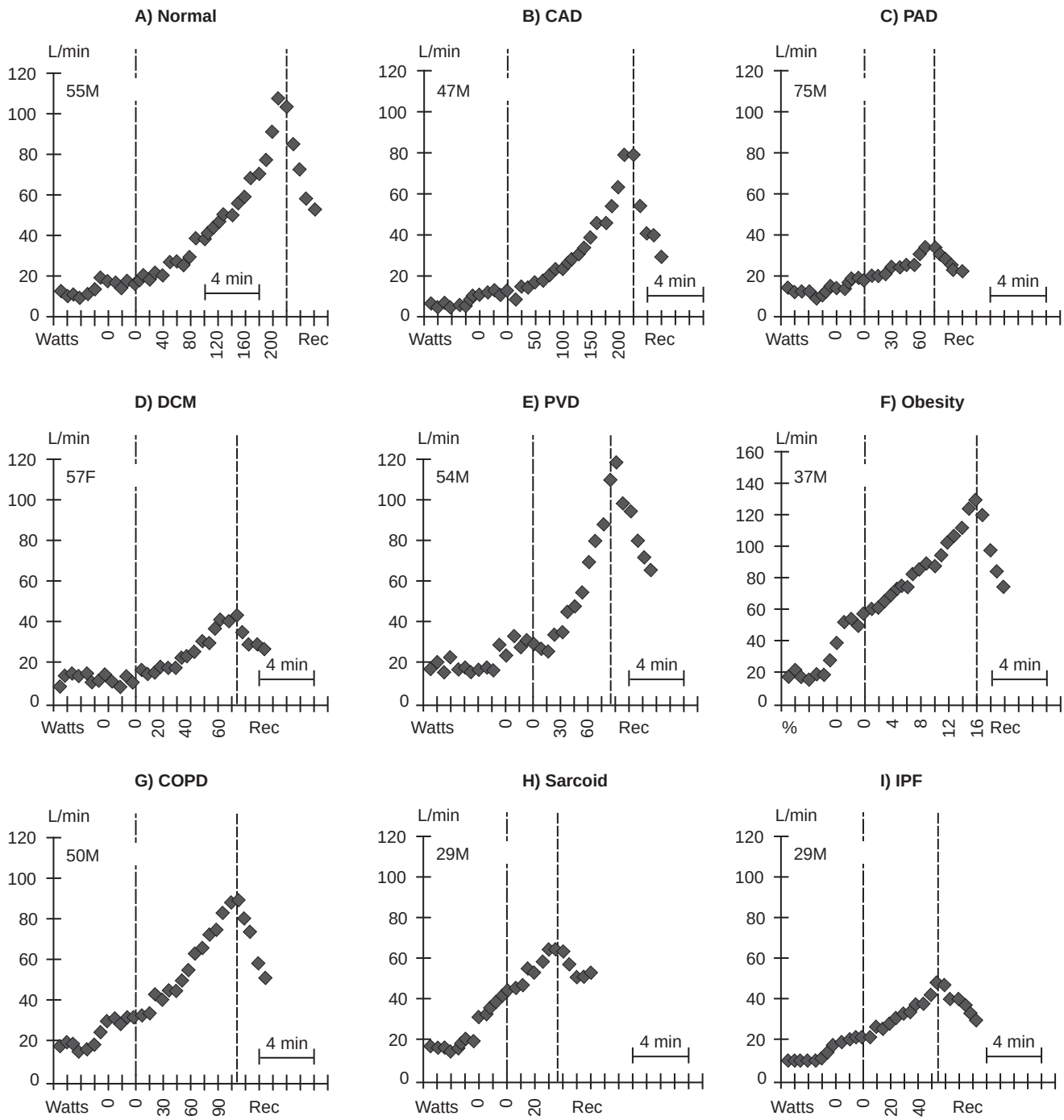

FIGURE 9.8. Plot of minute ventilation ($\dot{V}_E$, L/min-BTPS) as a function of time (1 minute between tick marks on *x*-axis) and work rate, for the same nine patients shown in Figure 9.1. The period of increasing work rate starts at the *left vertical dashed line* and ends at the *right vertical dashed line.*

(Fig. 9.8F), COPD (Fig. 9.8G), sarcoidosis (Fig. 9.8H), and IPF (Fig. 9.8I).

Respiratory Exchange Ratio at Rest, Increasing Work Rate Exercise, and Recovery

R as a function of time at rest, before the start of exercise, during increasing work rate exercise, and early recovery is shown in panel 8 of the nine-panel graphical array (Fig. 4.32). Figure 9.9 shows panel 8 for the nine patients illustrated in Figure 9.1. R, in resting steady state, is constrained to a value between 0.7 and 1.0 with an average value of 0.8. After the start of exercise, there is usually a slight dip in R, followed by an increase to a value <1.0, as muscle respiration contributes to a greater degree to total body R. R then becomes still steeper when bicarbonate

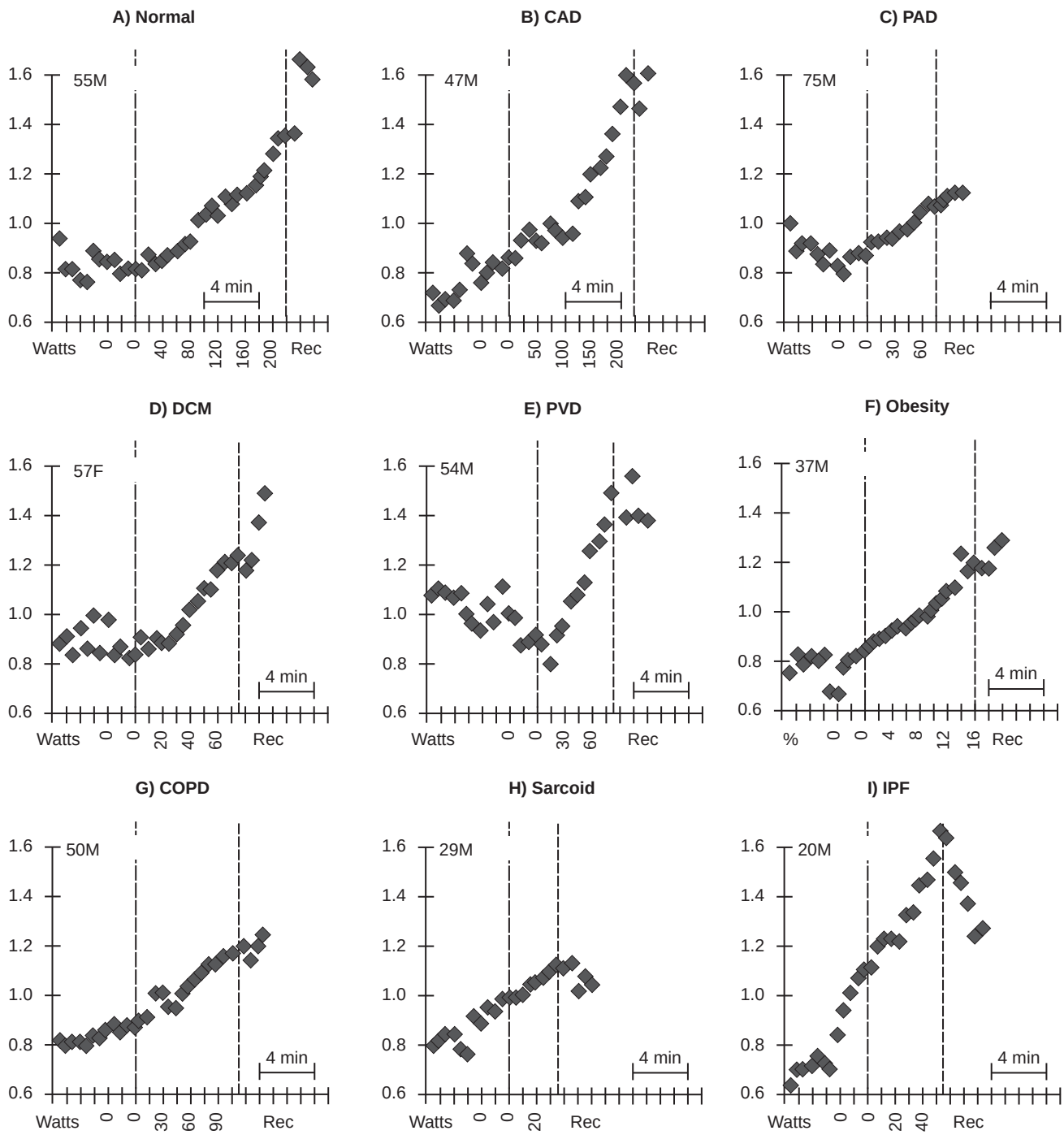

FIGURE 9.9. Plot of respiratory gas exchange ratio (R) as a function of time (1 minute between tick marks on *x*-axis) and work rate, for the same nine patients shown in Figure 9.1. The period of increasing work rate starts at the *left vertical dashed line* and ends at the *right vertical dashed line.*

starts buffering lactic acid, with the degree of steepening depending on the rate of lactic acid production and the ventilatory compensation for the metabolic acidosis. During the immediate recovery period, R normally increases because repayment of the O_2 debt is rapid, while CO_2 elimination remains high. The R is of particular importance in identifying patients who are hyperventilating at rest ($R > 1.0$). Also, R is useful in identifying those patients who are greatly cardiovascular limited. These patients commonly reveal a decreasing rather than an increasing R at the start of recovery (Fig. 9.9H, I).

Interpreting the nine panels of a case together provides important correlative data needed to properly interpret the changes in gas exchange accompanying each disorder. All of the panels have greater meaning when reviewed in relationship to each other.

DIAGNOSES UNIQUELY MADE BY CARDIOPULMONARY EXERCISE TESTING

Myocardial Dyskinesis Secondary to Myocardial Ischemia during Exercise

The normal contraction of the myocardium depends on the ability of all the myofibrils of the heart muscle to contract synchronously in response to the electrical depolarization set off by the sinoatrial pacemaker. With each heartbeat, ATP is consumed by the heart, primarily during systole, and regenerated in diastole when the myocardium is resupplied with oxygenated blood. For normal regeneration of ATP, the O_2 supply must be adequate. Because the diastolic period shortens as heart rate increases, there is less time to resupply O_2 to the myocardium. Thus exercise precipitates myocardial ischemia, primarily in regions of the heart that have impaired ability to resupply O_2 commensurate with the increased myocardial O_2 demand. The latter is dictated by the increase in cardiac work during exercise, which is proportional to the pressure-pulse rate product.

Asynchronous contraction of the myocardium would result in a reduction in stroke volume and a consequent failure of $\dot{V}O_2$ to increase in proportion to the increase in work rate, as illustrated in Cases 16–19 and 70 in Chapter 10. The slowing or failure of $\dot{V}O_2$ to increase with increasing work rate indicates that cardiac output is not increasing appropriately. When $\dot{V}O_2$ reaches a plateau despite increasing work rate, cardiac output has reached a maximum, despite a continuing increase in heart rate. Though cardiac output ($\dot{V}O_2$) has apparently stopped increasing despite heart rate continuing to increase, stroke volume (reflected in the reduced and nonincreasing O_2 pulse) must be decreasing, which is evidence of the myocardial dyskinesis of ischemia.

In patients with pathological ECG changes, with or without chest pain, simultaneous reduction in $\Delta\dot{V}O_2/\Delta WR$ and flattening of the O_2 pulse with increasing work rate and heart rate, strongly suggest development of myocardial ischemia during exercise. ECG changes suggestive of myocardial ischemia, without chest pain and without myocardial dyskinesis, make the diagnosis of myocardial ischemia questionable. By measuring gas exchange, the physician can confirm that myocardial dyskinesis did occur, as well as the $\dot{V}O_2$ and heart rate at which it occurred.

Chronic Heart Failure Due to Diastolic Dysfunction

Systolic dysfunction resulting in heart failure is usually easily diagnosed by the finding of a low ejection fraction and cardiomegaly. On the other hand, detecting heart failure due to diastolic dysfunction—a problem not uncommon in the elderly, patients with myocardial ischemia, heart transplant recipient patients, and patients with hypertrophic cardiomyopathy[54,66,68]—is difficult to diagnose because heart size and ejection fraction are normal. Without the clue provided by CPET and/or echocardiographic signs, critical objective measurements necessary to diagnose and quantify diastolic dysfunction may be absent.

On the other hand, in patients with chronic heart failure (whether due to systolic or diastolic dysfunction), noninvasive CPET can identify a reduced peak $\dot{V}O_2$ and *AT*, reflecting reduced O_2 transport, and when dysfunction is moderate to severe, an increase in $\dot{V}E/\dot{V}CO_2$ (impaired gas exchange efficiency). Because the increase in $\dot{V}E/\dot{V}CO_2$ is due to an increased VD/VT in proportion to the reduction in exercise tolerance, and is not accompanied by hypoxemia,[148] these findings must reflect decreased perfusion of ventilated lung and not airflow obstruction. Thus, CPET with gas exchange measurements is a test especially suited for making the diagnosis and quantifying chronic heart failure secondary to either systolic or diastolic dysfunction.

Pulmonary Vascular Occlusive Disease and Clinical Pulmonary Hypertension (Pulmonary Vasculopathy)

Most patients limited in exercise because of pulmonary vascular disease (pulmonary vasculopathy) have exertional dyspnea well before they have signs of pulmonary hypertension. Once signs of pulmonary hypertension are present, the patient has recruited all the pulmonary blood vessels normally reserved for recruitment during exercise. By this time, the clinical condition has seriously deteriorated, and the opportunity to intervene at an early stage of the disease with pulmonary vasodilator or anti-inflammatory treatment may be lost.

There is no noninvasive method other than exercise gas exchange, and possibly ventilation–perfusion

scans, capable of identifying a patient with a pulmonary vasculopathy at an early stage of the disease (i.e., when a patient is symptomatic but before pulmonary hypertension develops). This is because the patient's symptoms in early disease are present during exercise, not at rest. Although the pulmonary blood flow may be adequate at rest, these patients have difficulty in increasing pulmonary blood flow appropriately in response to exercise.

In patients with pulmonary vascular disease, $\dot{V}O_2$ usually does not continue to increase with a normal slope of 10 mL/min/W with progressive increases in work rate. Rather, the rate of rise gradually decreases (Fig. 9.1E) up to the point where continuation of exercise becomes intolerable, usually because of dyspnea or fatigue or both. $\dot{V}E$ relative to $\dot{V}CO_2$ is characteristically significantly elevated in patients with pulmonary vascular disease (Figs. 9.5E and 9.6E).

Referring to Figure 4.32, the peak $\dot{V}O_2$ (panel 1) and *AT* (panel 3), $\dot{V}E$–$\dot{V}CO_2$ relationship (panels 4 and 6), and $PETCO_2$ at the *AT* (panel 7) probably best quantify the severity of the illness[138,152] and may well prove to be the best guides for selection of patients with pulmonary vascular disease for aggressive medical therapy and lung transplantation. The steep heart rate rise and low O_2 pulse (likely reflecting a low stroke volume) will be evident in panels 2 and 3. The slope of $\dot{V}E$ plotted as a function of $\dot{V}CO_2$ (panel 6), which is about 25 in the normal individual, will be much higher in patients with pulmonary vascular disease (Fig. 9.5E, G–I). This increase depends primarily on the increase in VD/VT and the development of exercise hypoxemia.[142,149] Figure 9.6 shows high values for $\dot{V}E/\dot{V}CO_2$ at the *AT* or at the nadir of $\dot{V}E/\dot{V}CO_2$, reflecting decreased perfusion to ventilated lung (high $\dot{V}A/\dot{Q}$) and quantitatively related to the degree of pulmonary vascular occlusion. Arterial blood gases, displayed on panel 7 (Fig. 4.32), along with end-tidal O_2 and CO_2 and calculation of VD/VT, further characterize the abnormal physiological state of the pulmonary circulation.

Developing a Right-to-Left Shunt during Exercise

About 25% of the population have a potentially patent foramen ovale,[122] but this phenomenon is functionally unimportant unless right atrial pressure exceeds left atrial pressure. However, a rise in right atrial pressure sufficient to open a patent foramen ovale may develop during exercise in patients with primary pulmonary vascular disease (e.g., primary pulmonary arterial hypertension [PAH]) or pulmonary vascular disease secondary to lung or connective tissue diseases. Thus, a right-to-left shunt, absent at rest, may develop in these patients during exercise.

An opened patent foramen ovale allows venous blood to flow from the right to the left atrium when right atrial exceeds left atrial pressure. This will result in a rapid decrease in systemic arterial PO_2, while the increase in the CO_2 and H^+ load entering the systemic arterial circulation, stimulate the arterial ventilatory chemoreceptors. This phenomenon can occur despite normal or near-normal arterial oxyhemoglobin saturation at rest (see Case 35 in Chapter 10). An exercise test with 100% O_2 breathing allows quantification of an anatomical right-to-left shunt developing during exercise, when arterial blood is simultaneously sampled.

The diagnosis of a right-to-left shunt developing during exercise can be suspected from characteristic changes in gas exchange at the start of exercise.[136] Referring to the format of Figure 4.32, these changes include an abrupt decrease in $PETCO_2$ and increase in $PETO_2$ (panel 7) at the start of exercise, along with simultaneous abrupt increase in R (panel 8), $\dot{V}E/\dot{V}O_2$ (panel 4), and $\dot{V}E/\dot{V}CO_2$ (panel 4), reflecting hyperventilation of the pulmonary blood flow as compensation for the venous blood flowing through the foramen ovale (see Case 36 in Chapter 10). A decrease in arterial O_2 saturation at the start of exercise can usually be documented with a pulse oximeter (panel 7). The state of the shunt during exercise can be followed over time, without sampling of arterial blood for measurement of blood gases, by repeat CPET with particular attention paid to panels 4, 7, and 8.

An example of gas exchange abnormalities revealing the intermittent development of a right-to-left shunt during exercise is shown in Figure 9.10 in a sequential series of studies at 4-month intervals over a 16-month period during treatment with continuous intravenous epoprostenol. When blood begins to shunt from right to left during exercise, $\dot{V}E$ abruptly increases, with an increase in $\dot{V}E/\dot{V}CO_2$ (panel 4), rather than the usual decrease seen in normal subjects when exercise starts. The slope of $\dot{V}E$ as a function of $\dot{V}CO_2$ sharply increases at the work rate at which the blood starts to shunt right to left (see the $\dot{V}E/\dot{V}CO_2$ versus time and the $\dot{V}E$ versus $\dot{V}CO_2$ in test 1 of Fig. 9.10). The reason ventilation increases so steeply when the shunt develops is that arterial $[H^+]$ is regulated. Thus, shunting of high CO_2 and H^+ (primary ventilatory stimulants) blood from the venous system into the left side of the circulation bypasses the lungs.[123] When the shunted blood reaches the arterial and subsequently central chemoreceptors, ventilation is stimulated in proportion to the shunted CO_2 and H^+ load.

In test 2 (Fig. 9.10), the shunt no longer develops early in exercise because of a reduction in right atrial pressure. However, it did develop late in exercise. This abrupt ventilatory stimulus presumably forced the patient to stop exercise soon after the development of the right-to-left shunt. By test 3 (after 8 months of treatment), the pulmonary hypertension was much reduced, peak $\dot{V}O_2$ and O_2 pulse had increased, and the evidence for an exercise induced right-to-left shunt had disappeared. Now, and in the remaining two tests, $\dot{V}E/\dot{V}CO_2$ (third panel down) remained relatively constant, although abnormally elevated. This indicated that VD/VT was elevated, but relatively

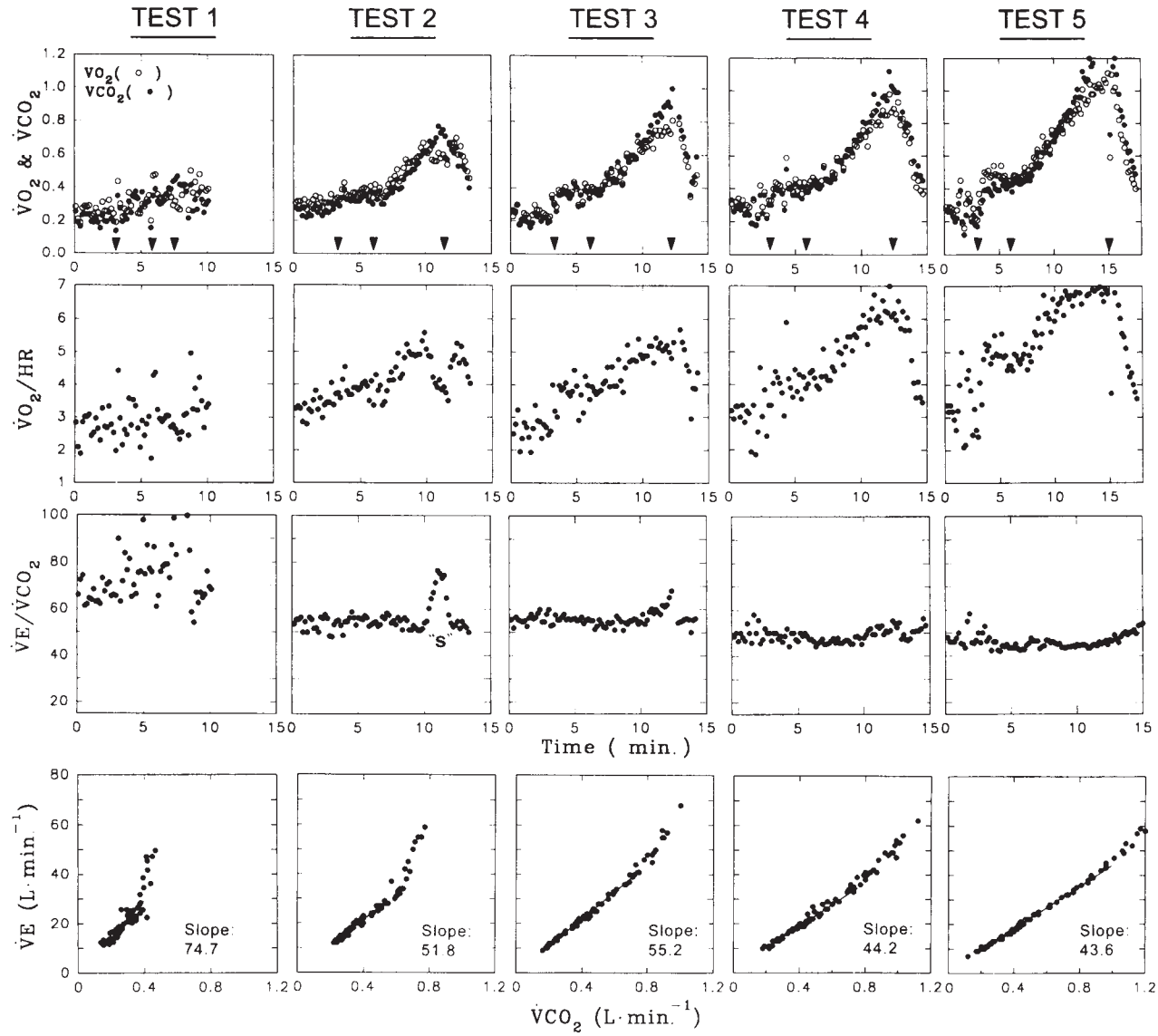

FIGURE 9.10. Five tests in a patient with primary pulmonary hypertension, each done at 4-month intervals. Test 1 was done as a control before the start of continuous intravenous epoprostenol, a preparation of prostacyclin. Test 2 was done after 4 months of treatment, and test 3 was done 4 months later, and so on, for a total of 16 months. Although the full nine-panel plots were obtained, for ease of comparing the physiological changes with time, only four panels of data are shown for each test. The top panel contains plots of $\dot{V}O_2$ and $\dot{V}CO_2$ (L/min) against time. On the abscissa of this plot are three arrows, the left indicating the transition from rest to unloaded cycling, the middle arrow indicating the start of the increasing exercise period, and the arrow on the right indicating the end of exercise. As is evident from this panel in test 1, the patient was very restricted and could perform very little exercise. At that time, her O_2 pulse (mL/beat) (second panel down) could not increase in response to exercise, indicating that the product of her stroke volume and arteriovenous O_2 difference was at its maximum. The ventilatory equivalents for CO_2 (third panel down) are very high at rest (first 3 minutes) and increase further after exercise starts due to the opening of a right-to-left shunt, presumably through the foramen ovale. This is reflected in a large change in the slope of $\dot{V}E$ versus $\dot{V}CO_2$ in the fourth panel down. The slope value shown in this panel is that for the lower slope before the diverting of blood through the right-to-left shunt. The slope value of 74.7 is very high (normal being about 25; see Chapter 7). This steep slope primarily reflects the poor perfusion to ventilated lung (increased V_D/V_T). The abrupt steepening of this slope reflects an increase in right-to-left shunt.

The repeat study 4 months after the start of treatment (test 2) shows a significant increase in peak $\dot{V}O_2$ and O_2 pulse and a reduced ventilatory response as evident from the decrease in $\dot{V}E/\dot{V}CO_2$ and in the lower slope of $\dot{V}E$ versus $\dot{V}CO_2$ (51.8 vs. 74.7). The latter two values indicate that perfusion to ventilated lung had become more uniform, although still quite abnormal. Just before the end of exercise, a right-to-left shunt developed, reflected in the abrupt decrease in $\dot{V}O_2$ and O_2 pulse and the increase in $\dot{V}E/\dot{V}CO_2$, designated by *S* in the third panel down, and the abrupt steepening of the slope of $\dot{V}E$ versus $\dot{V}CO_2$ in the fourth panel down.

The next three tests show improvement in all measurements, reaching a plateau response by the fifth test. Additional tests were done over the next 4 years and are not shown because there was no significant change from test 5. Thus, the patient is considerably improved and has become stable, but still has significant inability to increase cardiac output, as reflected by a reduced peak $\dot{V}O_2$ and O_2 pulse (60% and 70% of predicted, respectively) and elevated $\dot{V}E$ versus $\dot{V}CO_2$ slope and $\dot{V}E/\dot{V}CO_2$ at the anaerobic threshold.

fixed, presumably because of hypoperfusion of ventilated lung. However, shunting of venous blood into the arterial circulation no longer occurred.

This information about this patient's pathophysiology and change with treatment or time was obtained noninvasively and could not have been obtained as successfully even with more complicated invasive tests. More invasive and complex tests could not be repeated with the frequency and at the low cost of CPET. Exercise testing with gas exchange measurements allowed the treating physician to recognize that the patient, who was extremely ill when first seen, had improved sufficiently to be removed from the lung transplantation list. The patient has been studied for an additional 12 years with CPET-guided therapy.

Pulmonary Vascular Disease Limiting Exercise in Chronic Obstructive Pulmonary Disease

Although patients with COPD usually are exercise limited because of abnormal lung mechanics, as reflected by a low exercise breathing reserve, some are limited primarily by a reduced pulmonary capillary bed, which limits the increase in blood flow in response to exercise. In such a patient, lung reduction surgery might improve the lung mechanics but not improve exercise tolerance because pulmonary blood flow cannot increase beyond that achieved before surgery. Case 50 in Chapter 10 is an example of this problem. Exercise testing should therefore be done before lung reduction surgery, with the objective of confirming that impaired lung mechanics limits CO_2 elimination and pH regulation, not impaired systemic blood flow and O_2 transport.

Impaired Muscle Bioenergetics

Skeletal muscle enzyme defects affect exercise gas exchange. The gas exchange abnormality depends on the site of the muscle enzyme defect. Thus, a patient with a myopathy that affects myophosphorylase or one of the glycolytic enzymes (e.g., phosphofructokinase) would have a reduced maximum exercise tolerance because of the inability to develop a lactic acidosis and thereby benefit from the Bohr Effect, as described in Chapter 2. This will be reflected in exercise gas exchange,[51] not only by a reduced peak $\dot{V}O_2$ but also by failure to produce extra CO_2 from the buffering of lactic acid, as described by Riley et al.[114] In contrast, enzyme defects in the mitochondrial electron transport chain cause a lactic acidosis at a very low work rate,[50] with accompanying gas exchange abnormalities similar to those observed in patients with heart failure, except for the changes due to ventilation-perfusion mismatch.[21,22] Exercise studies are a good screening technique for detecting muscle enzyme defects affecting bioenergetics and are useful for objectively assessing therapeutic modalities.

Psychogenic Dyspnea and Behavioral Causes of Exercise Intolerance

How do physicians diagnose psychogenic dyspnea or behavioral causes (volitional or nonvolitional) of exertional intolerance? It is difficult to make these diagnoses reliably unless the patient is studied during exercise with quantitative gas exchange measurements.

These patients often undergo extensive diagnostic assessments, at great expense, that indirectly evaluate the cause of exercise intolerance. Without the diagnostic benefits of CPET, the physician may prescribe an irrelevant drug that only adds to the patient's problem (see Case 9 in Chapter 10). Obviously, to diagnose the cause(s) of exercise intolerance, the patient should be studied during exercise, and the essential variables that evaluate cellular and external respiration should be measured. Logically, CPET should be done before the patient undergoes expensive imaging studies and/or an extensive invasive workup that searches, in a state of rest, for an abnormality that takes place during exercise.

Volitional behavioral causes of exercise intolerance also require CPET to make or confirm this diagnosis (see online Cases 98 and 99 in Chapter 10). Thus, these diagnoses are only available to those physicians who learn how to use CPET and can interpret the results.

GRADING SEVERITY OF HEART FAILURE

Symptoms had been the primary method by which physicians graded severity of heart failure before the useful development of CPET. The New York Heart Association (NYHA) classification of severity of heart failure, based on symptoms, has been almost universally used for almost six decades.[97] It has four functional classifications (classes I to IV) based on the perceived activity level of the patient. Matsumura et al.[78] found that the NYHA classification correlated reasonably well with the *AT* and peak $\dot{V}O_2$, showing that symptoms and the ability to transport O_2 were correlated. However, the peak $\dot{V}O_2$ and *AT* had a relatively large range of values within a given NYHA class. This is thought to be due to differences in how patients perceive their symptoms and differences in how physicians interpret the severity of patients' described symptoms.

Because of this subjectivity, Weber and Janicki[151] sought a more objective assessment based on peak $\dot{V}O_2$ and *AT*. They established an A through D classification for progressive severity as a function of the decline in peak $\dot{V}O_2$/kg (Table 9.1). They found that this classification for objectively assessing cardiac dysfunction was superior to the NYHA classification. A consensus conference on prioritizing patients with heart failure for heart transplantation based on predicted survival time also agreed with this more objective assessment.[84]

TABLE 9.1

Weber's Exercise Functional Classification Based on Maximal Oxygen Uptake and Anaerobic Threshold

Class	$\dot{V}O_2$max (mL/min/kg)	*AT* (mL/min/kg)	Clmax (L/min/m^2)
A	>20	>14	>8
B	16–20	11–14	6–8
C	10–15	8–11	4–6
D	<10	<8	<4

$\dot{V}O_2$max, maximal or peak $\dot{V}O_2$; *AT*, anaerobic threshold; Clmax, maximal exercise cardiac index (cardiac output per square meter of body surface area).
(From Weber KT. Cardiopulmonary exercise testing and the evaluation of systolic dysfunction. In: Wasserman K, ed. *Exercise Gas Exchange in Heart Disease*. Armonk, NY: Futura Publishing; 1996:55–62, with permission.)

Stelken et al.[126] thought that the Weber–Janicki approach, although an advance, would be more satisfactory if it were normalized for age and gender as well as body size. They analyzed the normal predictive values based on size, age, and gender (described in Chapter 7) and found that the percent predicted peak $\dot{V}O_2$ was a good predictor of survival. Stevenson[127] and Gitt et al.[48] assessed prognosis by comparing peak $\dot{V}O_2$/kg without normalizing for age and gender with the percentage of predicted $\dot{V}O_2$, which itself normalizes for age, gender, and height. Both groups found that either method was a good predictor of survival. However, Gitt et al.[48] found that normalizing just to body weight gave a better assessment of prognosis than percent predicted $\dot{V}O_2$. Importantly, the physiological assessment (using peak $\dot{V}O_2$/kg) has been determined to be a more reliable independent predictor of survival than the NYHA symptom classification or measurements of ejection fraction.[73,76,85,126]

FICK PRINCIPLE CARDIAC OUTPUT DURING MAXIMAL EXERCISE FROM MEASURED PEAK OXYGEN UPTAKE AND ESTIMATED PEAK $C(a-\bar{v})O_2$

$\dot{V}O_2$ is equal to the cardiac output × $C(a-\bar{v})O_2$. The relationship is illustrated graphically in Figure 9.11. From this figure, it can be seen that exercise performance depends on the ability to extract O_2 from the arterial blood and to increase cardiac output. The ability to increase $C(a-\bar{v})O_2$ depends primarily on the hemoglobin concentration and arterial O_2 content. Given a normal hemoglobin concentration of 15 g/dL and normal arterial oxyhemoglobin saturation and content, the arterial O_2 content is approximately 20 mL per 100 mL. The maximal extraction is about 75% to 80%, resulting in a maximal $C(a-\bar{v})O_2$ at peak exercise of 15 to 16 mL per 100 mL. Thus, without increasing cardiac output, the maximum that $\dot{V}O_2$ can increase over resting is threefold. All further increase in exercise $\dot{V}O_2$ depends on increasing cardiac output.

Normal middle-aged subjects who are relatively sedentary have a peak $\dot{V}O_2$ about 10 times resting, and well-trained subjects can have peak $\dot{V}O_2$ values of 20 times resting. Thus, referring to Figure 9.11, peak $\dot{V}O_2$ reveals the magnitude of the increase in cardiac output in response to maximal exercise. If hemoglobin and arterial O_2 content are normal, a peak exercise $\dot{V}O_2$ that is only three times the resting value reveals that the patient is in the category of patients waiting for a heart transplant. In contrast, a sixfold increase in peak $\dot{V}O_2$ reveals that the patient can at least double his or her cardiac output in response to exercise. As the ability to increase cardiac output diminishes, $C(a-\bar{v})O_2$ has a greater influence on the $\dot{V}O_2$ increase in response to exercise. Consequently, measurement of $\dot{V}O_2$ increase in response to exercise provides critical information about the ability of cardiac output to increase.

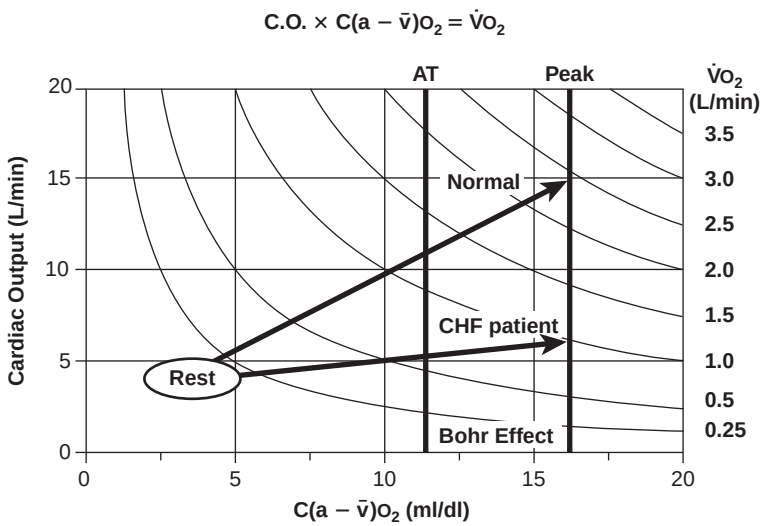

FIGURE 9.11. O_2 uptake guided measurement of cardiac output during exercise. Each $\dot{V}O_2$ isopleth is a product of cardiac output and arterial–mixed venous O_2 difference $[C(a-\bar{v})O_2]$. If $C(a-\bar{v})O_2$ can be estimated, such as at peak $\dot{V}O_2$ or at the anaerobic threshold (*AT*), cardiac output can be estimated at those points. The *arrows* illustrate how the values of $\dot{V}O_2$ at the *AT* and peak can be used to estimate the subject's cardiac output noninvasively. This graph also illustrates that the *AT* becomes a larger fraction of the peak $\dot{V}O_2$ the lower the peak $\dot{V}O_2$.

$C(a-\bar{v})O_2$ changes almost linearly from a predictable low value of 5 mL per 100 mL (normal) to 6 mL per 100 mL (heart failure) at rest to about 15 to 16 mL per 100 mL in fit normal subjects[130] (see Fig. 3.3) and 13 to 16 mL per 100 mL in patients with heart failure,[2,134,151] at maximal exercise when the hemoglobin concentration is normal. If we knew the change in $C(a-\bar{v})O_2$ over the range of $\dot{V}O_2$ increase from rest to peak, or at specific levels of exercise such as at the *AT* (see Fig. 4.6) or peak $\dot{V}O_2$, we could estimate cardiac output from the $\dot{V}O_2$ alone. For instance, if the $C(a-\bar{v})O_2$ values were approximately 12 mL per 100 mL and 15 mL per 100 mL at the *AT* and peak $\dot{V}O_2$, respectively, we could calculate the cardiac output and the stroke volume from the $\dot{V}O_2$ values at these two levels of exercise.

Variation of the relationship between $C(a-\bar{v})O_2$ and percent peak $\dot{V}O_2$ is small among normal subjects[130] and among patients with heart failure[4,134,151] when the hemoglobin is normal. But despite the linear change with respect to percent peak $\dot{V}O_2$ during incremental exercise, the absolute value of $C(a-\bar{v})O_2$ must vary with factors that affect oxyhemoglobin content in arterial and mixed venous blood. These factors are considered next.

Factors Affecting Arterial–Venous Oxygen Difference during Exercise

As noted in Chapters 3 and 4, cardiac output can be estimated noninvasively at peak exercise and the *AT* by using the Fick principle. Calculation depends on the measurement of peak or *AT* $\dot{V}O_2$ and a concurrent estimate of $C(a-\bar{v})O_2$. Stroke volume is estimated by dividing the derived cardiac output by heart rate, or O_2 pulse method (see Chapter 4).

The measurement of $\dot{V}O_2$ and heart rate and estimation of CaO_2 are straightforward. Because $C(a-\bar{v})O_2$ changes in a relatively linear and predictable way from rest to peak $\dot{V}O_2$,[4,130,134,151] it is possible to estimate $C(a-\bar{v})O_2$ from hemoglobin concentration and arterial oxyhemoglobin saturation given the parameter of 75% to 80% maximal extraction in mixed venous blood ($C\bar{v}O_2$). The assumptions for estimating $C(a-\bar{v})O_2$ should be valid unless exercise is terminated by other than circulatory factors, such as by ventilatory limitation, musculoskeletal disorders, poor motivation, peripheral arterial disease, or a defect in muscle bioenergetics, in which instances $C\bar{v}O_2$ would be abnormally high and $C(a-\bar{v})O_2$ would be abnormally low at maximal exercise because the normal maximal oxygen extraction does not take place.

Estimating Arterial–Venous Oxygen Difference

Estimates of $C(a-\bar{v})O_2$ at peak exercise are shown in Table 9.2. The estimates take into account the resting hemoglobin concentration and assume a hemoconcentration at peak exercise of 5% (see Fig. 2.36), an arterial oxyhemoglobin (O_2Hb) saturation of 96% (normal), a carboxyhemoglobin (COHb) saturation of 1% (normal), and a mixed venous O_2Hb saturation at maximal exercise of 24%. From these values, and recognizing that the hemoglobin O_2 binding capacity is 1.34 mL/g Hb, the estimated $C(a-\bar{v})O_2$ at peak exercise happens to be equal to the hemoglobin concentration itself (Table 9.2).

Adjustments in maximal $C(a-\bar{v})O_2$ can be made in subjects who are exceptionally fit or have disease. Corrections might be made for how fitness and disease affect hemoconcentration and mixed venous O_2Hb saturation at peak exercise. Also, corrections might be

Table 9.2

Estimation of Arteriovenous Oxygen Difference [$C(a-\bar{v})O_2$] at Peak Exercise

Hb (g/100 mL)[a]	O_2 capacity (mL/100 ml)	Arterial O_2 saturation (%)	Mixed venous O_2 saturation (%)	Arterial O_2 concentration (mL/100 mL)	Mixed venous O_2 concentration (mL/100)	$C(a-\bar{v})O_2$ (mL/100 mL)[b]
16	22.5	96	24	21.4	5.4	16.0
15	21.1	96	24	20.0	5.0	15.0
14	19.7	96	24	18.7	4.7	14.0
13	18.3	96	24	17.4	4.4	13.0
12	16.9	96	24	16.0	4.0	12.0
11	15.5	96	24	14.7	3.7	11.0
10	14.1	96	24	13.4	3.4	10.0

[a]The left column identifies the resting hemoglobin concentration. The hemoglobin concentration at peak exercise is considered to be 5% higher than the resting hemoglobin—that is, a fitness factor of 1.05 (see text for definition). The carboxyhemoglobin concentration is assumed to be 1%.
[b]Modifications: (i) If the person is very unfit, decrease the $C(a-\bar{v})O_2$ (right column) by up to 6%; if the person is very fit, increase the $C(a-\bar{v})O_2$ by up to 6%. (ii) Reduce the $C(a-\bar{v})O_2$ by 1% for each 1% increase in carboxyhemoglobin above 1%. (iii) Reduce the $C(a-\bar{v})O_2$ by 1% for each 1% decrease in arterial oxyhemoglobin saturation below 96%.

made for the effect of change in arterial O_2Hb content resulting from arterial O_2 desaturation (e.g., patients with lung diseases) and increased COHb (e.g., cigarette smokers).

Exercise Hemoconcentration

The degree of hemoconcentration (up to 10%) varies with the peak $\dot{V}O_2$ or fitness of the subject. The initial estimate shown in Table 9.2 is for a subject of average fitness and hemoconcentration (5%). For an exceptionally fit subject, the $C(a-\bar{v})O_2$ obtained from Table 9.2 should be increased by up to an additional 5%. In contrast, the $C(a-\bar{v})O_2$ should be decreased by up to 5% in the very unfit subject or the patient who has a very low peak $\dot{V}O_2$.

Mixed Venous Oxyhemoglobin Saturation

The $C(a-\bar{v})O_2$ shown in Table 9.2 is calculated for a subject with average fitness whose mixed venous O_2Hb saturation at peak exercise is 24%. However, mixed venous O_2Hb saturation can decrease at peak exercise to as low as 18% in the fit and be as high as 30% in disease. To apply the data in Table 9.2 to patients with different levels of fitness, increase $C(a-\bar{v})O_2$ by up to 6% in the very fit subject and decrease $C(a-\bar{v})O_2$ by up to 6% according to the patient's disease limitation.

Arterial Oxyhemoglobin Saturation

If the subject has hypoxemia, the $C(a-\bar{v})O_2$ determined from Table 9.2 should be decreased by 1% for each 1% decrease in arterial O_2Hb saturation below 96%.

Carboxyhemoglobin Saturation

If the subject has a COHb saturation greater than 1%, decrease the $C(a-\bar{v})O_2$ by the percentage of COHb saturation minus 1.

Examples of Estimating Arterial–Venous Oxygen Difference

The following examples illustrate how the initial estimate of $C(a-\bar{v})O_2$ from Table 9.2 is modified to take into account unusual fitness, arterial oxyhemoglobin desaturation, and increased COHb concentration.

Example A

If the resting Hb is 14 g per 100 mL of blood, the first estimate of $C(a-\bar{v})O_2$ is 14 mL O_2/100 mL blood (Table 9.2). If we consider the person to be very fit, we might find more hemoconcentration (from 5% to 8%) and a slightly lower mixed venous O_2 saturation (from 24% to 20%). In this case, the final estimate of $C(a-\bar{v})O_2$ would be $14 \times 1.07 = 15.0$ mL O_2/100 mL blood, instead of the 14 mL O_2/100 mL blood provided by the original estimate shown in Table 9.2.

Further, in this example, where the $C(a-\bar{v})O_2$ is 15.0 mL O_2 per 100 mL or 150 mL O_2 per liter of blood and the peak $\dot{V}O_2$ is 3,500 mL/min and heart rate is 170 beats per minute at peak exercise, the cardiac output at peak exercise is 3,500/150 = 23.3 L/min, and the concurrent stroke volume is 23,300/170 = 137 mL/beat.

Example B

If the resting Hb is 12 g per 100 mL of blood, the initial estimate of $C(a-\bar{v})O_2$ is 12 mL O_2/100 mL blood. For an extreme example, if we considered the person to be quite limited, we might estimate that there is less hemoconcentration (from 5% to 3%) and less decrease in mixed venous oxyhemoglobin saturation (from 24% to 30%). If, in addition, the SaO_2 is only 90% [leading to a 6% decrease in $C(a-\bar{v})O_2$] and the COHb is 5% [a further 4% decrease in $C(a-\bar{v})O_2$], then the final estimate of $C(a-\bar{v})O_2$ is $0.82 \times 12 = 9.8$ mL O_2/100 mL blood.

In this example, where $C(a-\bar{v})O_2$ is 98 ml O_2 per liter (9.8 mL per 100 mL blood) and the $\dot{V}O_2$ is 900 ml/min and heart rate is 160 at peak exercise, the cardiac output at peak exercise is 900/98 = 9.2 L/min, and the concurrent stroke volume is 9,200/160 = 58 mL/beat.

By referring to Figure 9.11, one can see the magnitude of the effect on the final estimate of cardiac output of taking into account these corrections of $C(a-\bar{v})O_2$. In general, the effect on the finally derived cardiac output measurement is relatively small, especially when peak $\dot{V}O_2$ is low.

Shortcut Estimate of Stroke Volume from Oxygen Pulse

The O_2 pulse is equal to the product of $C(a-\bar{v})O_2$ and stroke volume (SV). Therefore, stroke volume can be estimated at peak exercise by dividing the O_2 pulse at that time by the concurrent $C(a-\bar{v})O_2$, derived from Table 9.2. Thus, if the arterial oxyhemoglobin saturation is 96% (normal at sea level) and the resting hemoglobin concentration is 15 g/dl, and the maximum O_2 pulse is 15, the maximum stroke volume would be 100 ml ($SV = 15/15 \times 100$). If the O_2 pulse is 25, the stroke volume would be 167 ml ($SV = 25/15 \times 100$). Thus, the maximum O_2 pulse provides a convenient shortcut for estimating the concurrent stroke volume.

CARDIOPULMONARY EXERCISE TESTING FOR EVALUATING PROGNOSIS

Because the most reliable work rate domain for cardiac output estimation from $\dot{V}O_2$ appears to be during submaximal work (e.g., near the lactic acidosis threshold), this observation was applied clinically to calculate cardiac output and predict outcomes in patients after anterior myocardial infarction (AMI). Bigi et al.[20] studied

46 patients with AMI: 39 male and 7 female patients aged 55 ± 8 years (mean ± SD) with an ejection fraction of 39 ± 7%. Each subject underwent CPET and coronary angiography following hospital discharge. The estimated cardiac output was calculated using the linear regression of arterial–venous oxygen content against percent $\dot{V}O_2$max (see Fig. 3.6).[130]

Cardiac output at the *AT* of less than 7.3 L/min was the best cutoff value for identifying multivessel CAD (relative risk = 3.1). Angiographic scores were significantly higher in patients with a cardiac output at the *AT* of less than 7.3 L/min and were inversely and significantly correlated to cardiac output at the *AT*. Moreover, cardiac output at the *AT* of less than 7.3 L/min was associated with an increased risk of further cardiac events (odds ratio = 5; 95% confidence interval = 1.4–17) and was a significant discriminator of survival for the combined end point of cardiac death, reinfarction, and clinically driven revascularization.

For cardiac output at the *AT* estimated by this method for normal subjects and patients with left ventricular failure, see Figure 4.6. Cardiac output at the *AT* determined from CPET appears to be a safe and useful measurement for providing additional diagnostic and prognostic information in patients with CAD. From the studies reported later in this chapter, this statement could be extended to patients with left ventricular failure, primary pulmonary hypertension, and COPD.

Prognosis in Heart Failure and Prioritizing Patients for Heart Transplantation

Exercise testing makes a variety of contributions to the understanding of exercise impairment and exertional dyspnea in chronic heart failure.[135] A number of investigators have found that measurements of cardiac function at rest, both invasive and noninvasive, are poorly predictive of patients' symptoms, exercise capacity, prognosis, or need for heart transplantation. Weber et al.[150] compared resting cardiac function with exercise capacity in patients with heart failure and found that such variables as cardiac index, left ventricular ejection fraction, wedge pressure, and radiographic heart size correlated poorly with measured peak $\dot{V}O_2$. Neither resting nor exercise pulmonary capillary wedge pressure correlated significantly with peak $\dot{V}O_2$. However, peak $\dot{V}O_2$ did correlate with maximum cardiac output during exercise, as should be expected. Matsumura et al.[78] and Itoh et al.[65] showed that peak $\dot{V}O_2$ and *AT* correlated with symptom scores as measured by NYHA class. Mean *AT* was 90% ± 15%, 77% ± 14%, and 60% ± 12% of the predicted values for NYHA class I, class II, and class III, respectively, in the study of Itoh et al.[65] *AT* correlated only weakly with resting left ventricular ejection fraction measured by echocardiogram or angiography.

Weber[150] suggested a new classification of heart failure based on peak oxygen uptake and *AT*, as shown in Table 9.1. Koike et al.[71] similarly linked exercise capacity to symptom score. In these patients, peak $\dot{V}O_2$, *AT*, $\Delta\dot{V}O_2/\Delta$WR, and maximum WR decreased as NYHA symptom scores worsened. NYHA class III patients had a maximum $\dot{V}O_2$ averaging 17 ± 3 mL/min/kg, *AT* of 11 ± 2 mL/min/kg, $\Delta\dot{V}O_2/\Delta$WR equal to 6.2 ± 2 mL/min/watt, and maximum work rate of 98 ± 22 W.

Szlachik et al.[140] reported that patients with peak $\dot{V}O_2$ of less than 10 mL/min/kg had a 77% 1-year mortality; if peak $\dot{V}O_2$ was between 10 and 18 mL/min/kg, mortality at 1 year was only 14%. In a study by Rickenbacher et al.,[110] 116 consecutive patients with severe but stable congestive heart failure referred for heart transplantation were studied in close follow-up with medical management. This group demonstrated a very good prognosis, with actuarial survival at 1 year of 98% and at 4 years of 84%. The mean peak $\dot{V}O_2$ was 17.4 ± 4.3 mL/kg/min for the group as a whole. These authors concluded that stable symptoms and a relatively high peak exercise $\dot{V}O_2$ identified patients with a favorable prognosis despite a very low resting ejection fraction.

Some remarkable clinical trials have led to exercise testing for providing critical criteria in predicting survival and therefore in prioritizing patients for cardiac transplantation.[38] A prospective study by Mancini et al.[76] randomized patients referred for heart transplantation into the following groups: those with peak $\dot{V}O_2$ greater than 14 mL/kg/min who were considered too well for transplantation, those with peak $\dot{V}O_2$ less than 14 mL/kg/min who were accepted for transplantation, and those with peak $\dot{V}O_2$ less than 14 mL/kg/min who were not accepted for surgery for noncardiac reasons. If peak $\dot{V}O_2$ was greater than 14 mL/kg/min, then 1-year survival was 94%. Those patients with peak $\dot{V}O_2$ below 14 mL/min/kg had a 70% 1-year survival with medical management. The prognostic value of these criteria was not appreciably improved when peak $\dot{V}O_2$ was expressed as a percentage of predicted.[1] Deaths and complications were also predicted by a peak $\dot{V}O_2$ of less than 14 mL/kg/min in a study by Roul et al.[116]

Osada et al.[96] identified 154 of 500 congestive heart failure patients referred for cardiac transplantation, with a peak $\dot{V}O_2$ equal to or less than 14 mL/min/kg. They found that 3-year survival rate was reduced from 83 to 55% in those patients unable to reach a systolic blood pressure of 120 mm Hg.

Stevenson et al.[128] presented data on 68 heart transplantation candidates (peak $\dot{V}O_2$ less than 14 mL/min/kg) who had repeat exercise tests at a mean 6 ± 5 months after the initial evaluation. The purpose of the repeat exercise test was to determine the possibility of removing the patient from the heart transplantation list, following a period of medical therapy. All of these patients were vigorously treated with diuretics and afterload reduction and were advised to become involved in informal exer-

cise rehabilitation training. Thirty were without "major" improvement, but 38 had an increase in peak $\dot{V}O_2$ of more than 2 mL/min/kg, to a value greater than 12 mL/kg/min. Of these, 7 patients reported no clinical improvement, but 31 were clinically improved. The improvement group also had improved *AT*, peak O_2 pulse, and exercise heart rate reserve, and a decrease in resting heart rate. In the 31 patients removed from the heart transplantation waiting list, the actuarial survival rate was 100%.

Myers et al.[85] reported the results of studies on 644 patients with chronic heart failure over a 10-year period. They found that peak $\dot{V}O_2$ outperformed right heart catheterization data, exercise time, and the usual clinical variables used to assess heart failure patients in predicting outcome. They concluded that direct measurement of $\dot{V}O_2$ should be made when clinical or surgical decisions need to be made in patients referred for evaluation of heart failure or for consideration of heart transplantation.

Although most studies normalized the peak $\dot{V}O_2$ to body weight and ignored the variables of age and gender, Stelken et al.[126] compared the sensitivity of percentage of predicted peak $\dot{V}O_2$ based on weight, age, and gender, using the predicted values described in Chapter 7. In 181 ambulatory patients with NYHA class II to III symptoms, peak $\dot{V}O_2$, percent predicted peak $\dot{V}O_2$, and *AT* were significantly different for survivors and nonsurvivors when compared at 12 and 24 months. A total of 89 patients with a peak $\dot{V}O_2$ of less than 50% predicted had 1- and 2-year survival rates of 74% and 43%, respectively, compared with 98% and 90% for the 92 patients who had a peak $\dot{V}O_2$ greater than 50% predicted. Although Stelken et al.[126] found the percent predicted value to be a better predictor of survival than that of $\dot{V}O_2$/kg, Gitt et al.,[48] making the same comparison, found that normalizing to body weight was a better predictor. The difference might be due to the relative obesity factor in the two populations and its effect on the $\dot{V}O_2$/kg parameter.

Prognosis in Heart Failure Based on Peak Oxygen Uptake, Anaerobic Threshold, and $\dot{V}E/\dot{V}CO_2$ Ratio

Since the late 1980s, heart transplant cardiologists have appreciated that peak $\dot{V}O_2$ more sensitively predicts prognosis than more classic heart failure risk factors such as left ventricular ejection fraction, NYHA class IV symptoms, and neurohormonal markers (Table 9.3). Increasing experience has confirmed the prognostic value of peak $\dot{V}O_2$ in the evaluation of patients with heart failure for cardiac transplantation.[36,73,75,84,85,96,126,127] The 1993 Bethesda Conference for Cardiac Transplantation[84] concluded the indications for heart transplantation shown in Table 9.3. A low peak $\dot{V}O_2$ was the primary criterion, provided that at peak $\dot{V}O_2$, anaerobic metabolism had been reached (i.e., exercise above the *AT*).

Table 9.3

Bethesda Conference: Indications for Heart Transplantation

I. Accepted indications for transplantation
   A. Maximal $\dot{V}O_2$ less than 10 mL/kg/min with achievement of anaerobic metabolism
   B. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty
   C. Recurrent symptomatic ventricular arrhythmias refractory to all accepted therapeutic modalities

II. Probable indications for cardiac transplantation
   A. Maximal $\dot{V}O_2$ less than 14 mL/kg/min and major limitation of the patient's daily activities
   B. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty
   C. Instability of fluid balance and/or renal function not due to patient noncompliance with regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction

III. Inadequate indications for transplantation
   A. Ejection fraction less than 20%
   B. History of functional class III or IV symptoms of heart failure
   C. Previous ventricular arrhythmias
   D. Maximal $\dot{V}O_2$ greater than 15 mL/kg/min without other indications

(From Mudge GH, Goldstein S, Addonizio LJ, et al. Task force 3: recipient guidelines/prioritization. *J Am Coll Cardiol*. 1993;22:1–64, with permission.)

Because peak $\dot{V}O_2$ might be underestimated due to reduced patient effort as well as by premature termination of exercise by the examiner, Gitt et al.[48] and Sun et al.[137] studied the submaximal criteria of *AT* and $\dot{V}E$ versus $\dot{V}CO_2$ slope below the ventilatory compensation point (VCP) compared with peak $\dot{V}O_2$, normalized to both body weight and percent predicted, as measures of heart failure severity based on survival.

The *AT* reflects the maximal sustainable $\dot{V}O_2$ and is an objective parameter of cardiopulmonary exercise capacity. It can be derived from submaximal exercise testing and therefore does not require maximal patient effort. Another submaximal CPET measurement that has been found to have prognostic value for survival is the $\dot{V}E$ versus $\dot{V}CO_2$ slope below the VCP (see Fig. 4.20).[33,69] Gitt et al.[48] compared the peak $\dot{V}O_2$ and the submaximal parameters as predictors of 6-month and 24-month patient survival rate in a cohort of 223 patients. Thresholds were peak $\dot{V}O_2$ of less than 14 mL/min/kg; *AT* of less than 11 mL/min/kg; and $\dot{V}E$ versus $\dot{V}CO_2$ slope below the VCP

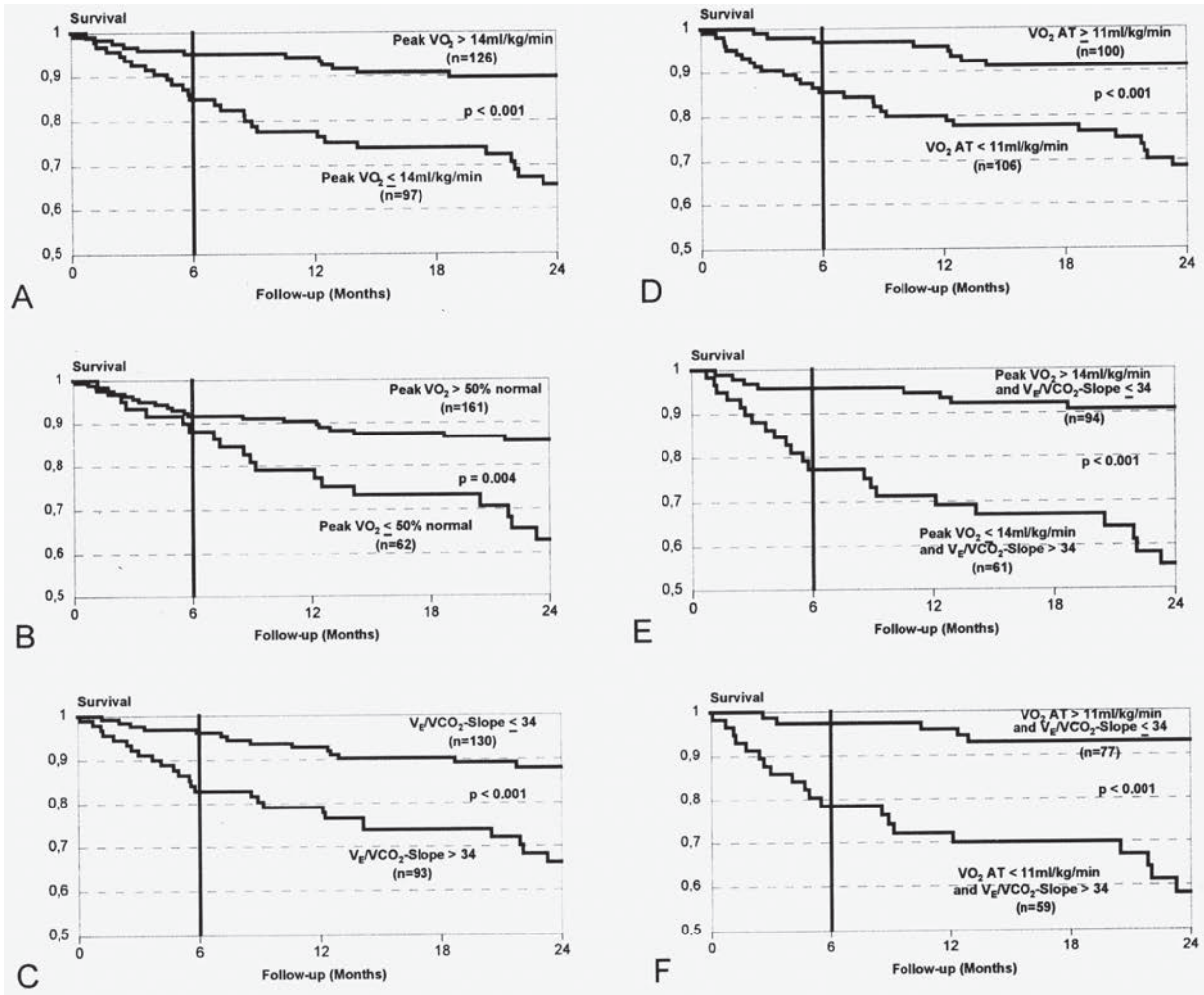

FIGURE 9.12. Kaplan–Meier survival curves using peak $\dot{V}O_2$ ≤14 **(A)**, peak $\dot{V}O_2$ <50% predicted normal **(B)**, $\dot{V}E$ versus $\dot{V}CO_2$ slope >34 **(C)**, $\dot{V}O_2$ at the anaerobic threshold (*AT*) <11 mL/kg per minute **(D)**, the combination of peak $\dot{V}O_2$ ≤14 and $\dot{V}E$ versus $\dot{V}CO_2$ slope >34 **(E)**, as well as $\dot{V}O_2$ at *AT* <11 and $\dot{V}E$ versus $\dot{V}CO_2$ slope >34 **(F)** as cutoff points. Significant differences in survival were found at 6 months after the initial evaluation in A, C, D, E, and F. (From Gitt AK, Wasserman K, Kilkowski C, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation.* 2002;106:3079–3084, with permission.)

of more than 35 for high risk. They found that each of these parameters separates the high-risk from the low-risk patients (Fig. 9.12).

Figure 9.13 shows the odds ratio of early death when these parameters are in the high-risk range. The combination of *AT* and $\dot{V}E$ versus $\dot{V}CO_2$ below the VCP was found to be the best predictor of early death (within 6 months) in patients with left ventricular failure, using the threshold criteria selected in this study. Because both *AT* and $\dot{V}E$ versus $\dot{V}CO_2$ below the VCP are determined at submaximal work levels and are not effort dependent, these are exceptionally valuable measurements. Sun et al.[137] confirmed the 6-month findings showing increased early death or hospitalization rates if values where beyond the threshold values for severity described above. When adding oscillatory breathing pattern in assessing

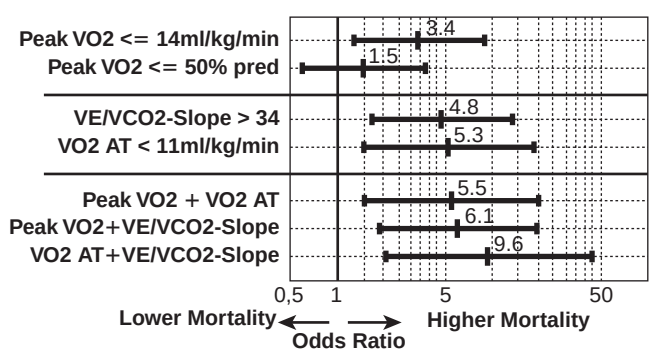

FIGURE 9.13. Cardiopulmonary predictors of early death within 6 months: univariate analysis. Numbers are odd ratios. Bars are 95% confidence interval. (From Gitt AK, Wasserman K, Kilkowski C, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation.* 2002;106:3079–3084, with permission.)

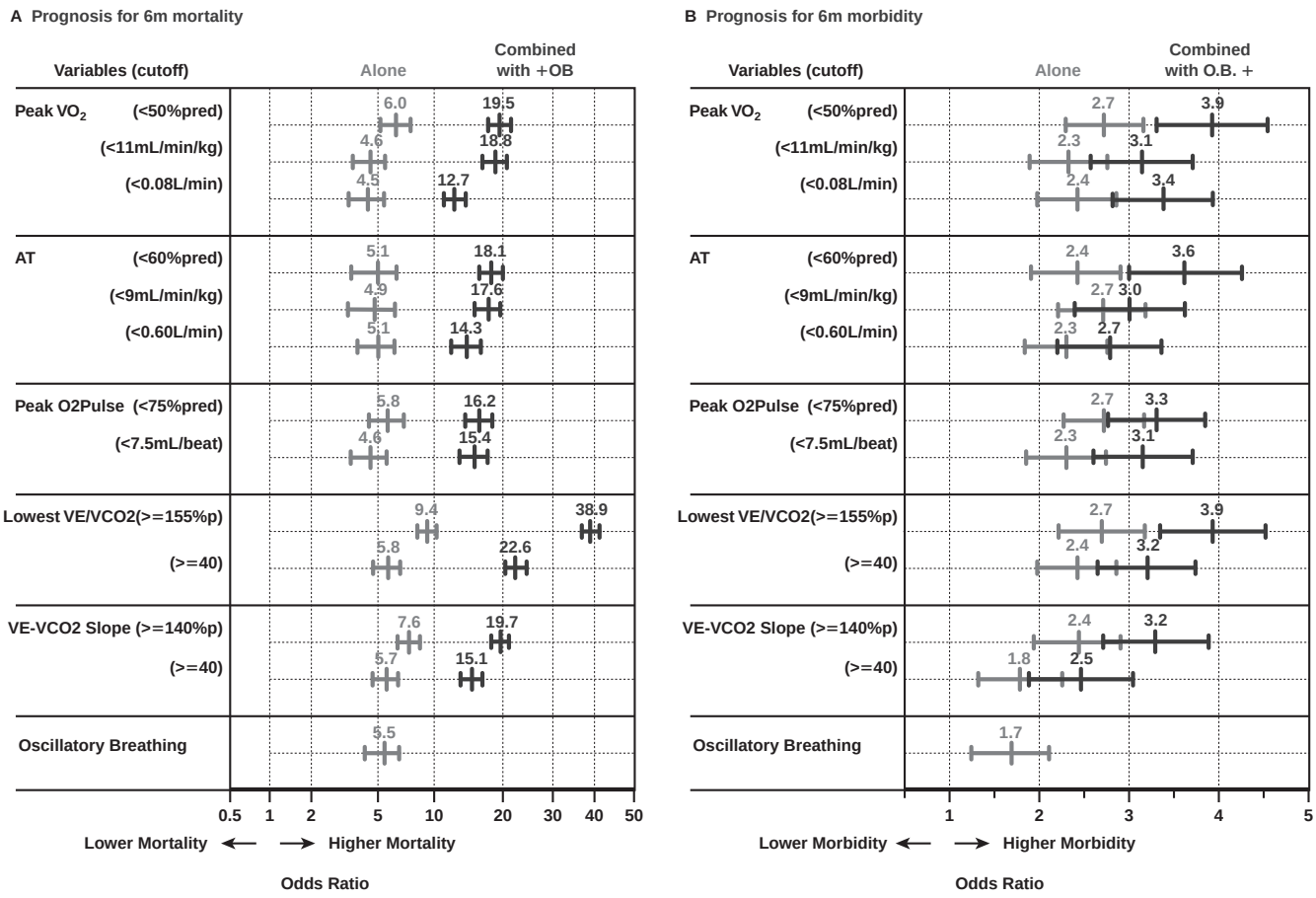

FIGURE 9.14. Odds ratio (OR) of cardiopulmonary exercise testing (CPET) variables, alone and combined with positive oscillatory breathing pattern (+OB), for 6-month mortality (**A**) and morbidity (**B**) in patients with NYHA class III systolic left ventricular heart failure. **A:** The odds ratio (OR) on the left show the mean and 95% confidence intervals of the individual CPET measurements, while the bars at the right are OR for the CPET measurements combined with oscillatory breathing pattern (+OB). The ORs for all CPET measurements and +OB alone and combined are significant. When each CPET parameter was combined with +OB, the OR values were significantly increased ($P < .05$ to $P < .001$). The best single predictor of 6 month mortality was the lowest $\dot{V}E/\dot{V}CO_2$ (≥155% predicted) (OR = 9.4) and the best combination is lowest $\dot{V}E/\dot{V}CO_2$ (≥155% predicted) with +OB (OR = 38.9). **B:** Although the OR values are lower, the trend agrees with the mortality data. (From Sun XG, Hansen JE, Beshai JF and Wasserman K. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. *J Am Coll Cardiol.* 2010;55:1814–1823, with permission.)

survival in stable patients with heart failure, death and early hospitalization rates within 6 months were even more marked (Fig. 9.14).

Prognosis in Primary Pulmonary Hypertension and Prioritizing Patients for Lung Transplantation

In patients with PAH who are unresponsive to pulmonary vasodilator therapy, lung transplantation is the only way of lowering the pulmonary vascular resistance. The decision to remove a patient's lung and replace it with a lung from a cadaver or a living donor is a critical decision. Importantly, it needs objective documentation that the medical pulmonary vasodilator therapy is not working and that the disease is so severe that the patient is at imminent risk of dying without this major surgical intervention (one that will subsequently require lifelong medical immunosuppressive therapy). Thus, reliable quantitative evaluation of the ability to increase pulmonary blood flow under exercise stress is essential. Wensel et al.[152] reported that reduced peak $\dot{V}O_2$ was a prognosticator of early death from PAH. But exercise test parameters that monitor the specific pathophysiology of PAH have not been evaluated as prognostic indicators.

Sun et al.[138] studied the exercise pathophysiology in a cohort of 64 patients with PAH and showed that peak O_2 uptake decreases in proportion to worsening NYHA symptom class. However, symptoms are too variable with

respect to function to be relied upon for making the decision to resort to lung transplantation. The physiological measurements used to evaluate impairment severity include the following:

1. Peak $\dot{V}O_2$, which is proportional to the peak pulmonary blood flow
2. *AT*, which reflects the maximum sustainable O_2 uptake
3. O_2 pulse, which is equal to the stroke volume × $C(a-\bar{v})O_2$
4. $\Delta\dot{V}O_2/\Delta WR$, which reveals the ability to increase pulmonary blood flow with increasing work rate
5. $\dot{V}E/\dot{V}CO_2$ at the *AT* or lowest value between the *AT* and VCP, which provides an index of the degree of $\dot{V}A/\dot{Q}$ mismatch

These were all highly significant when correlated with symptoms.

Despite the existence of these excellent noninvasive descriptors of the abnormalities found in pulmonary hypertension, they have not been systematically used to prognosticate survival or select patients for lung transplantation. However, we have found that those patients with PAH with the shortest survival tend to have the lowest peak $\dot{V}O_2$, *AT*, and $PETCO_2$ at the *AT* and the highest $\dot{V}E/\dot{V}CO_2$ at the *AT*. From this experience and that of Wensel et al.,[152] we believe that objective physiological measurements should be used to decide if and when the lung should be transplanted in patients with primary pulmonary hypertension.

Prognosis in Chronic Obstructive Pulmonary Disease and Prioritizing Patients for Lung Reduction Surgery

Oga et al.[87] analyzed the relations among exercise capacity, health status, and mortality rate in 150 male patients with stable COPD with a mean postbronchodilator forced expiratory volume in 1 second (FEV_1) of 47.4% of predicted. Each patient was studied with pulmonary function testing, progressive cycle ergometry exercise testing with gas exchange, and health status questionnaires[67] at entry into the study. In a 5-year follow-up, 31 had died. Multivariate Cox proportional hazards analysis revealed that the peak oxygen uptake was predictive of mortality independent of FEV_1 and age. Stepwise Cox proportional hazards analysis revealed that the peak $\dot{V}O_2$was the most significant predictor of early mortality, of the made measurements. Hiraga et al.[57] also studied the relationship between physiological parameters (derived from CPET) and survival time, over a 3- to 5-year period in 120 patients with COPD; they had similar findings to Oga et al.[87]

The recently concluded National Emphysema Treatment Trial in the United States,[43] the focus of which was treatment with pulmonary rehabilitation alone or with rehabilitation and lung reduction surgery, revealed that the only patient group that benefited from the surgery was the group with upper lung field emphysema and reduced exercise tolerance (40 W/min or less at peak). If the patient did not have reduced exercise tolerance, regardless of the distribution of the emphysema, surgical resection did not improve the prognosis or exercise tolerance of the patient.

PREOPERATIVE EVALUATION OF SURGICAL RISK

Evaluating relative risk of major surgery, particularly in the elderly, has been an important recent application of CPET. Older et al.,[88] Ridgway et al.,[111] and Wilson et al.[155] have shown that the ability of the heart, lungs, pulmonary and the peripheral circulations to support an increased metabolic rate in the postoperative period can be evaluated by preoperative CPET. A patient's capacity to increase oxygen delivery during exercise has been shown to correlate with the capacity to maintain organ system function after surgery. Exercise testing, especially determination of the $\dot{V}O_2$ at the *AT* (the threshold of sustainable $\dot{V}O_2$), has been shown to be useful in identifying high-risk surgical patients, including those judged to have normal cardiopulmonary function by clinical assessments and measurements made at rest. CPET is useful, particularly in evaluating the elderly prior to surgery, for identifying patients with unsuspected heart or lung disease, and those with decreased organ system function.

Thoracic Surgery

Patients being considered for thoracotomy, usually for resection of lung cancer, are at particular risk of postoperative complications. CPET has been suggested as a valuable adjunct because spirometry, radionuclide scanning, and arterial blood gases have not been completely successful in identifying all high-risk patients and, most important, may miss patients with significant cardiovascular disease.[46,82,90–92,132,145] In addition, because resectional surgery remains the most effective therapy for lung cancer, exercise testing may identify patients who are likely to tolerate resection even though their poor resting lung function would otherwise preclude surgery.

Smith et al.[124] retrospectively reported 22 patients who underwent elective thoracotomy and found 11 who had postoperative respiratory failure, myocardial infarction, arrhythmias, lobar atelectasis, pulmonary embolism, or death. These 11 patients had a significantly lower mean peak $\dot{V}O_2$ than those without complications after surgery. A total of 91% of patients with complications had a peak $\dot{V}O_2$ during cycle exercise of less than 20 mL/kg/min. In this study, six of six patients who had a peak $\dot{V}O_2$ of less than 15 mL/min/kg and four of six patients who had a peak $\dot{V}O_2$ of 15 to 20 mL/min/kg had complications. Similarly, a peak $\dot{V}O_2$ of less than 10 mL/kg/min identified the two patients

who died and the majority of postoperative complications among 50 patients reported by Bechard and Wetstein.[15]

Bolliger et al.[23] found that peak $\dot{V}O_2$ during cycle ergometry, expressed as percent predicted, was predictive of postresection complications such as CO_2 retention, prolonged mechanical ventilation, myocardial infarction, pneumonia, pulmonary embolism, and death. In a group of 80 patients, 8 of 9 patients with peak $\dot{V}O_2$ of less than 60% predicted had complications, whereas only 8 of the remaining 71 patients had complications. When patients had a peak $\dot{V}O_2$ greater than 75% of predicted, 90% were complication free. The same group found that a peak $\dot{V}O_2$ less than 10 mL/kg/min was associated with 100% mortality.[64] Patients with complications had a lower mean peak $\dot{V}O_2$ (10.6 ± 3.6 mL/kg/min vs. 14.8 ± 3.5 mL/kg/min).

A prospective study by Morice et al.[83] provided additional evidence for the value of exercise testing in "high-risk" patients undergoing thoracotomy. A total of 37 patients had been considered inoperable because of a low FEV_1 (<40% predicted), an anticipated postsurgical FEV_1 of less than 33% predicted, an abnormal radionuclide scan, or an arterial PCO_2 more than 45 mm Hg. Thirteen patients who underwent exercise testing had a peak $\dot{V}O_2$ greater than 15 mL/kg/min. Eight of these patients subsequently had resectional surgery. Although mean FEV_1 was poor in this group (mean 40% of predicted), six of eight patients had an uncomplicated course, and all patients were discharged within 22 days of surgery. This study suggests that even some high-risk patients, based on resting lung function, can be more objectively assessed with data from exercise testing.

Abdominal Surgery

Older et al.[89] found, in a retrospective study of elderly patients undergoing major abdominal surgeries, that the *AT* obtained during CPET was particularly valuable in identifying postoperative complications. In 187 patients aged over 60 years, mean $\dot{V}O_2$ at the *AT* averaged 12.4 ± 2.7 mL/min/kg. If the *AT* was less than 11 mL/min/kg (found in 30% of the study patients), mortality from cardiovascular complications was 18%. On the other hand, if the *AT* was greater than 11 mL/min/kg, the cardiovascular death rate in the postoperative period was only 0.8%. Of interest, those patients who manifested evidence of myocardial ischemia in addition to having an *AT* of less than 11 mL/min/kg had a 42% mortality rate.

In a later prospective study of 548 patients over 60 years of age (or younger, if the patient was known to have ischemic heart disease), Older et al.[88] used the *AT* determined during CPET to separate high from low risk for mortality following major surgery. Based on their earlier retrospective study, they used an *AT* of 11 mL/min/kg as the threshold for separating high from low risk. Patients were triaged to the ward for routine care if their *AT* was greater than 11 mL/min/kg, they had no ECG evidence of myocardial ischemia, and their $\dot{V}E/\dot{V}O_2$ at the *AT* was less than 35. This represented 51% of the total population studied. None of these patients died of cardiovascular causes. A total of 21% (115 patients) of the population studied had an *AT* greater than 11 mL/min/kg, but also had either ECG evidence of myocardial ischemia or a $\dot{V}E/\dot{V}O_2$ at the *AT* of more than 35—a change found with heart failure. They were admitted to the intermediate care unit. Of this population, 1.7% (2 patients) died of cardiovascular causes. The remaining 28% (153 patients) of the starting population were identified as high risk based on an *AT of less than 11 mL/min/kg or aortic or esophage*al surgery. These were triaged to the intensive care unit and had a 4.6% cardiovascular system mortality. Thus, use of CPET to determine the high-risk patient for major surgery allowed the services to use their high-care units for those people who were most ill and identified patients at low risk, as assessed by CPET, to be admitted directly to the ward.

Who Should Undergo Cardiopulmonary Exercise Testing Preoperatively?

Several questions remain about the use of CPET in preoperative evaluation. First, who are the most suitable candidates? It is unlikely that all patients need to be tested, but patients with suspected cardiopulmonary disease (especially cardiac disease) may be confirmed with testing. It does appear important to offer exercise testing to older patients and those with marginal lung or cardiac function who would otherwise be excluded from major thoracic or abdominal surgery as being at too high a risk for surgical complications. Good exercise capacity may translate into surprisingly low postoperative risk.

Second, there is the question about the type of exercise testing to be performed for preoperative evaluation. Measurements of peak $\dot{V}O_2$ and $\dot{V}O_2$ at the *AT* provide objective data that can be used to identify high- and low-risk populations. There is a question of how useful CPET is in comparison with more simple tests with less sophisticated measurements, such as stair climbing or timed walking tests.[42,59]

Third, there is further need to focus on postoperative complications relating to specific types of surgery and on CPET that reveals the most limiting organ system. Results of exercise testing in patients have been largely used in those undergoing thoracic (lung) and abdominal surgery. The value of exercise testing for predicting complications of other forms of surgery, such as heart or vascular surgery or orthopedic procedures, has not been determined. Finally, there is a need for more evidence that improvement in preoperative exercise capacity by smoking cessation, medical therapy, exercise training, or other interventions can reduce postoperative risks.

MEASURING IMPAIRMENT FOR DISABILITY EVALUATION

Exercise testing has an important role in impairment and disability evaluation. Sometimes, the focus is on establishing causation of disease from a substance encountered in the workplace; in other cases, the process is to determine the degree of impairment.

Impairment and Disability

The term *impairment*, as used in the United States, is a measurable, objective decrease in functional capacity. *Disability* is an assessment of the impact of impairment on the individual and requires socioeconomic and environmental input, including factors such as age, gender, education, economic and social environment, and energy requirements of the occupation.[108] A World Health Organization statement[157] defined impairment as "any loss or abnormality of psychological, physiological, or anatomical structure or function," while disability was defined as "any restriction or lack (resulting from impairment) of ability to perform an activity within the range considered normal for a human being." Physicians are asked to identify and measure impairment. Although opinions are often sought about a patient's disability, such decisions are usually made through an administrative or legal process. Exercise testing permits objective measurement of physiological function, thereby determining impairment, not disability.

CPET is indicated when a precise measurement of work capacity (work rate, peak $\dot{V}O_2$, or the *AT*) is required, or when symptoms or subjective exercise capacity are inconsistent with resting measurements. The greatest potential advantages may be in evaluating people with one disorder (e.g., heart disease, peripheral arterial disease) coexisting with another (e.g., lung disease, increased blood carboxyhemoglobin from cigarette smoking or $\dot{V}A/\dot{Q}$ abnormality from pulmonary vascular occlusive disease in whom ventilatory drive is exceptionally high). In the case of the latter, mild to moderate defects in ventilatory mechanics might be sufficient to create intolerable dyspnea during mild exercise. In some patients, exercise capacity may be limited by a mechanism other than impairment in ventilatory mechanics detected by resting pulmonary function testing. Exercise-related abnormalities of arterial blood gases or increased dead space–tidal volume ratio may identify subtle evidence of respiratory disease as a cause of exercise limitation.

Problems in Assessing Impairment from Only Resting Measures

In 1986, the American Thoracic Society statement on evaluation of impairment and disability secondary to respiratory disorders recommended a systematic evaluation process.[108] The statement was "concerned primarily with impairments related to reduced lung function," and presented a rating system for impairment from lung disease based on forced vital capacity (FVC), FEV_1, FEV_1/FVC, and single breath diffusing capacity for carbon monoxide (DLCO). It also implied that there was a well-documented relation between measurements made at rest (e.g., FEV_1 and DLCO) and measurements made during exercise (peak $\dot{V}O_2$ and work capacity). The authors concluded that the majority of subjects undergoing an evaluation for impairment would not require exercise testing.

This conclusion can be challenged, however, by considering whether maximum work capacity can be predicted from resting pulmonary function. In this analysis, begin by assuming that a subject's FEV_1 = 1.5 L. If FEV_1 is used to predict maximum exercise minute ventilation ($\dot{V}E$) by using two reported estimates ($FEV_1 \times 35$ and $FEV_1 \times 40$),[26,45] the maximum $\dot{V}E$ values would range from 52.5 L/min to 60 L/min. Next, assume that dead space–tidal volume ratio (VD/VT) at maximum exercise ranges from a low of 0.15 in a normal subject to 0.40 in someone with moderate ventilation–perfusion mismatching from lung disease. Using this range, the estimated maximum alveolar ventilation [$\dot{V}A = \dot{V}E \times (1 - VD/VT)$] would range from 31.5 to 51 L/min for the maximum $\dot{V}E$ values calculated from the FEV_1 values above. Then, assuming that $PaCO_2$ is between 25 to 35 mm Hg (not unusual numbers), one could estimate the extremes of $\dot{V}CO_2$ that could be present by the following equation:

$$\dot{V}CO_2 \text{ L/min (STPD)} = PaCO_2 \times \dot{V}A \text{ L/min (BTPS)}/863$$

The estimated $\dot{V}CO_2$, using these example figures, ranges from 0.91 to 2.10 L/min.

Finally, what is the relationship between $\dot{V}CO_2$ and $\dot{V}O_2$? It is $\dot{V}O_2 = \dot{V}CO_2/R$, and R at maximum exercise ranges from 0.9 to 1.2. Therefore, our hypothetical subject's maximum $\dot{V}O_2$ might be as low as 0.76 L/min or as high as 2.33 L/min for the same FEV_1.

In conclusion, although the *ventilatory capacity* of the respiratory system for ventilation may be successfully predicted from resting FEV_1 (and this, too, is open to question), the *ventilatory requirement* for a given level of work cannot be predicted from the resting pulmonary function measurements.

Exercise Testing and Impairment Evaluation

A number of investigators have emphasized the usefulness of integrative CPET for determination of impairment.[3,5,39,61,77,93,95,99,115,131,154] Exercise testing complements clinical evaluation and adds to resting pulmonary func-

tion and imaging studies. It increases diagnostic accuracy both quantitatively (measurement of work capacity, peak $\dot{V}O_2$, progressively increasing and sustainable work capacity) and qualitatively (identification of the cause of exercise limitation).

During an approximate 3-year period, we had the opportunity to see 490 current or retired shipyard workers.[93] Of this population, 348 men who had complaints of exercise limitation or who were suspected of having exercise limitation were studied using 1-minute incremental cycle ergometry exercise with gas exchange measurements. A conclusion was made by the physician referring the patient for exercise studies as to the likelihood of exercise limitation, if any, and the specific organ system limiting exercise. This determination was based on chest roentgenograms, resting pulmonary function tests, resting ECG, medical history, physical examination, and smoking history (Fig. 9.15), but not CPET. Following CPET, another conclusion was made, but this time using all data acquired during the evaluation, including the exercise test (Fig. 9.15).

On the initial assessment, 148 subjects were predicted to have normal work capacity, but 46 of these subjects (31%) turned out to have a peak $\dot{V}O_2$ below the 95% confidence limit. The accuracy of the clinical prediction of a low work capacity was similar: 66 subjects were expected to have low work capacity; of these, only 43 (67%) were correctly categorized. Furthermore, the referring physicians could not judge whether the work capacity was normal or reduced in 134 subjects (38.5% of the total were evaluated to be; indeterminate) without CPET.

Following CPET, 60% of the indeterminate group were found to have a normal peak $\dot{V}O_2$, while 37% had an abnormally low peak $\dot{V}O_2$. Although the magnitude of reduction of peak $\dot{V}O_2$ had a significant correlation with resting pulmonary function (VC, FEV_1, DLCO as percent predicted), prediction of reduced work capacity from resting pulmonary function was often unhelpful. Overall, 138 workers had abnormally low peak $\dot{V}O_2$. Of these, 43 were correctly predicted to be impaired without CPET, while a further 46 were incorrectly predicted to be normal without CPET, and 49 who had impairment by CPET were indeterminate without it (Fig. 9.15). The sensitivity of resting pulmonary function tests, chest roentgenograms, and other studies for detecting low peak $\dot{V}O_2$ was only about 31%.

The cause of exercise limitation may not be reflected in resting studies, largely because the most often used resting data are the tests of pulmonary function. Among our 138 subjects with low peak $\dot{V}O_2$, only 25 were limited by obstructive or restrictive lung diseases, whereas in 95 (69%) of 138 cases, the exercise limitation was due to cardiovascular diseases (Table 9.4). The presence of a high proportion of cardiovascular disease in this patient

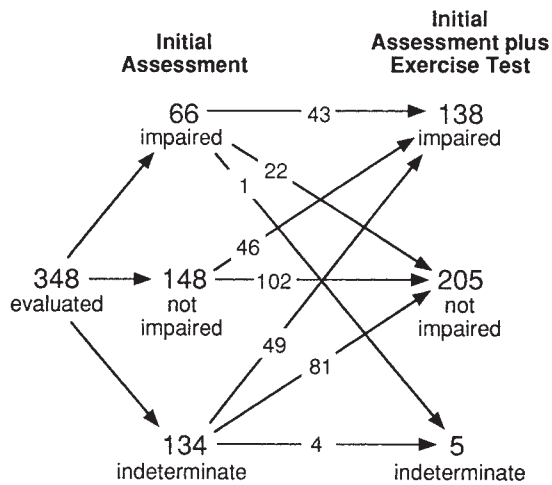

FIGURE 9.15. The influence of cardiopulmonary exercise testing on the evaluation of work impairment; 348 patients were initially referred for suspicion of functional impairment secondary to asbestos exposure. The initial assessment was done without exercise testing but with all other clinical modalities available to the evaluating physician. This assessment concluded that 66 were impaired, but no decision could be reached on 134 of the 348 patients being evaluated. In the final assessment, cardiopulmonary exercise data were added to the information available to the physician rendering the interpretation. This new information confirmed (cardiopulmonary exercise testing taken as the gold standard) impairment in 43 of the 66, with 22 going into the "not impaired" category and 1 into the indeterminate category. In contrast, 95 subjects were added to the impaired category: 46 from the "not impaired" category and 49 from the indeterminate category; 102 of the 148 subjects thought to be not impaired were confirmed as being not impaired. However, 81 were added to this category from the indeterminate category and 22 from the impaired category, making a total of 205 subjects for whom it was thought that there was no basis on which to conclude that the patient had a physiological impairment in the ability to perform physical work. Only 4 of the 130 subjects whose impairment was uncertain before cardiopulmonary exercise testing remained in this category after the cardiopulmonary exercise test.

TABLE 9.4

Percentage of Diagnostic Causes of Reduced Work Capacity in 138 Workers with Impairment

69% cardiovascular
41% cardiac
28% peripheral arterial or other
14% airway obstruction
4% restrictive lung disease
11% neurologic or musculoskeletal
2% obesity

Impairment is defined as peak $\dot{V}O_2$ below the 95% confidence limit of predicted.
(From Oren A, Sue DY, Hansen JE, et al. The role of exercise testing in impairment evaluation. *Am Rev Respir Dis.* 1987;135:230–235, with permission.)

population is not unique; Agostoni et al.[3] also found that 37% of 120 asbestos workers had unexpected cardiac limitation rather than ventilatory limitation.

Oxygen Cost of Work

In approximate terms, the oxygen cost ($\dot{V}O_2$) for office work might be about 5 to 7 ml/kg/min, for moderate labor about 15 ml/kg/min, and for strenuous labor 20 to 30 ml/kg/min (see Appendix E, Table E.4). Some guidelines suggest, in addition, that workers can perform manual labor at a comfortable work pace when this was approximately 40% of predicted peak $\dot{V}O_2$, a value approximating the lactic acidosis threshold in sedentary normal subjects.

Having obtained measurements of peak $\dot{V}O_2$ and the $\dot{V}O_2$ at the *AT*, it might be tempting to relate these to the oxygen cost of specific work tasks. A number of sources of information about specific O_2 costs of various physical activities, occupations, and specific kinds of movements exist, but these are estimates (see Appendix E, Table E.4). For given individuals who differ in age, weight, gender, rate of work, efficiency of movement, or degree of intermittency of the work task, the true metabolic cost of work ($\dot{V}O_2$) may vary greatly. For this reason, we recommend that the predicted metabolic cost of particular tasks be used as broad estimates rather than providing precise task-specific metabolic costs.

EXERCISE REHABILITATION

Physiological Basis of Exercise Rehabilitation

Endurance exercise training is commonly used to improve exercise tolerance and quality of life. It has proved useful in healthy subjects (including athletes) and in a number of patient groups. It is widely conceded that an exercise-training regimen is the most beneficial portion of rehabilitation programs. CPET is uniquely suited to gauge the specific benefits of exercise training. In addition, CPET serves to rule out coexisting disease processes that could contraindicate a rigorous exercise program. CPET also helps one to understand the physiological changes induced by the exercise training.

The benefits of exercise training may include the following:

1. Increasing muscle mass and mitochondrial number
2. Improving the distribution of blood and therefore O_2 flow to the contracting muscle, thereby reducing the cardiac (heart rate) stress
3. Reducing lactic acid production, resulting in a decrease in CO_2 and H^+ production and ventilatory drive at a given work rate
4. Improving the patient's sense of well-being

The general physiological changes in response to training are discussed in the following sections.

Skeletal Muscle

Skeletal muscles are composed of two major varieties of contractile cells.[118] One type of fiber seems designed for prolonged repetitive contraction. These fibers are known as type I, oxidative, or slow-twitch fibers. The other fiber type has rapid contractile properties but has a limited capacity for prolonged repetitive contraction; these fibers are known as type II, glycolytic, or fast-twitch fibers. The relative proportion of these two fiber types varies from muscle group to muscle group in a given subject and for the same muscle in different subjects.

After an effective program of training, subpopulations of type II fibers remodel. The type IIb (or IIx) fibers have a very low capacity for oxidative metabolism and have the ability to remodel into type IIa fibers,[8] which have a higher oxidative potential—in some ways similar to type I fibers. Type I fibers undergo extensive biochemical and structural modification.[119] In these fibers, the mitochondrial number and size increase. The concentrations of a number of enzymes in both the cytosol and the mitochondria increase.[60] These enzymatic changes facilitate the Krebs cycle reactions and oxidative phosphorylation so that the capacity to oxidatively metabolize the end product of glycolysis (pyruvate), fatty acids, and ketone bodies is increased.[119] In parallel with the increased ability to utilize oxygen, the ability to supply oxygen by improved blood flow to the muscle cells increases. Myoglobin levels in the trained type I muscle are higher[98]; this may contribute to the ability to transport oxygen from the muscle capillary to the site of metabolism. If muscle capillaries proliferate out of proportion to the increase in muscle fiber size,[120] the diffusion distance from the oxygen source (hemoglobin in the muscle capillary) to the oxygen sink (the mitochondrion in the muscle cell) may allow a given level of oxygen consumption to be sustained at a lower capillary P_{O_2}.

These structural and biochemical changes are seen only in the muscle groups involved in the training regimen[53]; this is known as the *principle of specificity*.[80] For example, walking or running does not induce such changes in the arm muscles. Training on a stationary bicycle will not fully translate into improvements in running performance because a somewhat different group of muscles is involved.

Changes in organ systems other than the exercising muscles also occur. The cardiovascular system undergoes significant changes as a result of exercise training.[35,80,117] The heart hypertrophies with increases in both ventricular wall thickness and chamber size. Body composition usually changes as a result of an effective program of

endurance training.[101,102] Muscle size increases and is reflected by an increase in lean body mass. Body fat often decreases more than muscle mass increases, so that body weight falls (although changes in body weight vary).

Cardiac Output and Heart Rate

After an effective program of training in normal subjects and patients who had been physically inactive for prolonged periods, cardiac output at peak exercise is increased, although cardiac output at rest may not be appreciably altered. However, stroke volume is higher at rest, at any given work rate, and at peak exercise. Consequently, heart rate at rest and at a given level of exercise is distinctly lower after exercise training, although peak heart rate is unchanged. Both systolic and diastolic blood pressure tend to be lower after training, especially in the hypertensive subject. Training may not increase cardiac output and stroke volume in patients with heart disease. However, heart rate is reduced at a given work rate after training, presumably due to better blood flow distribution to the working muscles and perhaps improved capillarization of muscle fibers, allowing an increase in O_2 extraction.[16,72,79,106]

Blood Lactate

After an effective program of endurance training, the remodeling of the exercising muscles yields both improved oxygen delivery to the more densely distributed mitochondria and improved mitochondrial capability for aerobic metabolism. As a result, the onset of anaerobic metabolism is delayed. At any given work rate above the pretraining *AT*, blood lactate levels are lower after exercise training (Fig. 9.16).[30,31] Sullivan et al.[133] demonstrated that knowledge of peak $\dot{V}O_2$ and *AT* allowed good prediction of an individual's blood lactate level in response to a given level of constant work rate exercise.

Oxygen Uptake

Endurance training increases maximal $\dot{V}O_2$, both because arteriovenous O_2 content difference widens and maximal cardiac output increases.[102] In healthy subjects, improvements on the order of 8% to 15% are commonly seen. During incremental exercise tests at below-*AT* work rates, $\dot{V}O_2$ is not altered appreciably by training. Differences are difficult to appreciate for typical ramp-type incremental exercise tests (the overall $\Delta\dot{V}O_2/\Delta WR$ slope remains approximately 10 mL/min/W).

Effective exercise training results in more rapid phase II $\dot{V}O_2$ kinetics, thereby reducing the magnitude of the oxygen deficit and the size of the slow (phase III) rise in $\dot{V}O_2$ in response to heavy constant work rate exercise. The decrease in the size of the phase III response is in close proportion to the decrease in blood lactate elicited by training.[30] Despite this close correlation, the mechanism of the decreased oxygen requirement remains controversial.[105]

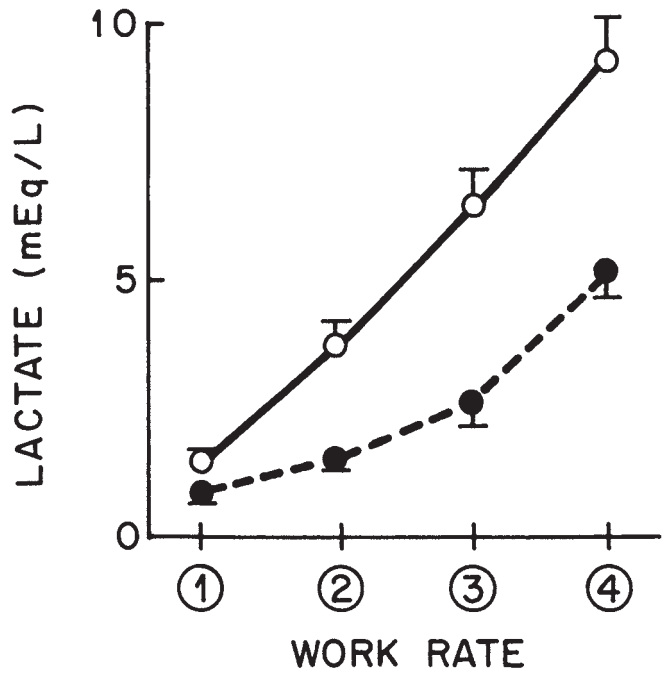

FIGURE 9.16. Effect of endurance training on end-exercise blood lactate levels at four work rates. Values plotted are the average (± standard error) responses of 10 subjects before (*solid line*) and after (*dashed line*) endurance training. Subjects exercised for 15 minutes at work rates ranging from moderate (work rate 1) to very heavy intensity (work rate 4). After training, blood lactate levels are lower in response to identical exercise tasks. (From Casaburi R, Storer TW, Ben-Dov I, et al. Effect of endurance training on possible determinants of $\dot{V}O_2$ during heavy exercise. *J Appl Physiol.* 1987;62: 199–207, with permission.)

Ventilation

In both the steady state and during exercise transients, $\dot{V}E$ responds in close proportion to CO_2 output.[32] After training, at a given work rate, $\dot{V}E$ is lower in proportion to the decrease in CO_2 output, the latter primarily due to the reduced HCO_3^- buffering of lactic acid. Moreover, because lactic acid production is lower, the hydrogen ion stimulation of the carotid bodies is reduced, resulting in less hyperventilation at a given heavy work rate.[31] This means that arterial PCO_2 is higher at a given heavy work rate above the *AT*. Figure 9.17 shows the responses to 15 minutes of exercise at four progressively higher work rates before and after a program of endurance training. At higher (above *AT*) work rates, there is a dramatically lower ventilatory response to exercise.

Other Physiological Responses

Blood catecholamine and other hormonal responses to a given level of heavy exercise are often dramatically lower

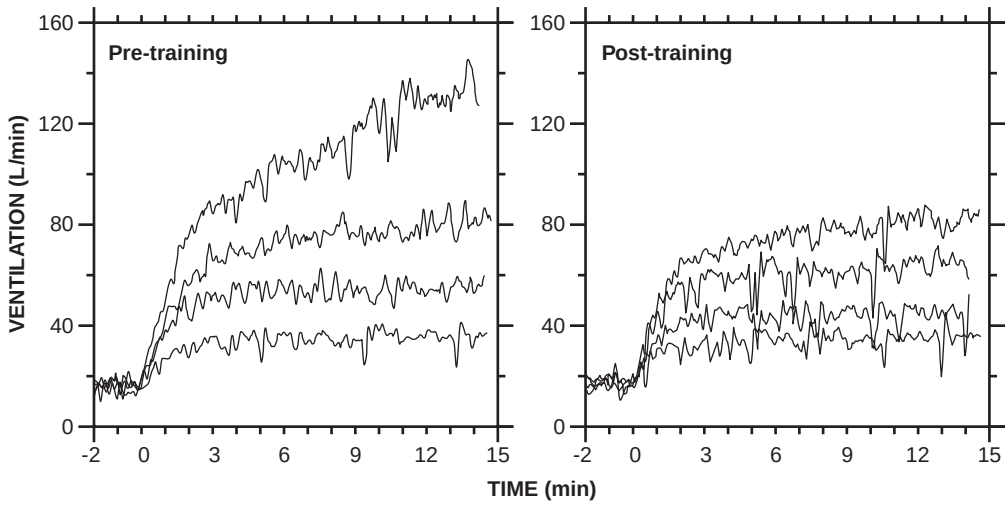

FIGURE 9.17. Effect of endurance training on the breath-by-breath time course of ventilation following the onset of constant work rate exercise in a healthy subject. **Left:** Pretraining responses to 95, 148, 191, and 233 W. **Right:** Posttraining responses to identical work rates after 8 weeks of endurance training. Note the dramatic decrease in ventilation at the higher work rates after training. (From Casaburi R, Storer TW, Ben-Dov I, et al. Effect of endurance training on possible determinants of $\dot{V}O_2$ during heavy exercise. *J Appl Physiol.* 1987;62:199–207, with permission.)

after training,[139,156] although the fractional reduction varies appreciably among subjects.[30] The body temperature increase that occurs with exercise is attenuated.[30,47] The rating of perceived exertion is also generally reduced.[56] The extent to which this reduction is predominantly linked to improved physiological function or to psychological factors is unclear.[49]

Exercise Rehabilitation in Heart Disease

The objective of exercise training is to improve both exercise tolerance and quality of life. Because patients with heart disease become physically inactive as a result of reduced ability to deliver blood to the muscles of locomotion, the skeletal muscles undergo change characteristic of detraining. The American Heart Association Committee on Exercise, Rehabilitation, and Prevention[100] wrote a comprehensive statement on the role of exercise in chronic heart failure (HF). In contrast to the practice up until about 25 years ago, when patients with HF were put to bed to *rest* their hearts, patients with heart failure are now put on exercise training programs. The statement summarizes many studies showing the benefits of exercise training, in which exercise tolerance and peak $\dot{V}O_2$ are increased, the latter by 12% to 31%, depending on the study and the particular training schedule employed. The training effect was, however, consistently correlated with the duration of the program. No significant exercise-related complications were reported. Despite the consistent increase in peak $\dot{V}O_2$ and exercise tolerance with training found in patients with HF, no consistent echocardiographic changes are demonstrable.

Although it has not been demonstrated that catecholamines consistently decrease with exercise training in patients with HF, Casaburi et al.[30] demonstrated that, in normal subjects, exercise training did induce striking reductions in blood catecholamine concentration at work rates above the pretraining *AT*. As in normal subjects (Fig. 9.16), exercise training reduces the lactate, and its accompanying H^+, response to exercise in patients with HF. Consequently, ventilatory drive, as in normal subjects, is also decreased in these patients in response to exercise training (Fig. 9.17).[31,107] However, in contrast to the predominant mechanism for the decrease in $\dot{V}E$ with training in normal subjects, which is attributable to the decrease in lactic acid production, some of the decrease in $\dot{V}E$ in HF might be attributed to a decrease in the often markedly elevated VD/VT. Some investigators also attribute the decrease in $\dot{V}E$ to attenuation of an abnormally stimulated ergoreflex originating in skeletal muscle.[103]

Exercise training results in a decrease in heart rate in response to a given exercise O_2 uptake. Some of this reduction in heart rate might be due to an increase in stroke volume, as reported in some studies, but most is thought to be due to peripheral changes and better perfusion and extraction of O_2 by the muscles involved in the exercise. When cardiac function and ability to increase cardiac output improve, the changes in muscle that came about due to inactivity might be reversed. Thus, the contribution of muscle atrophy to the exercise limitation might be rectified with exercise training.

With that logic in mind, Itoh and Kato[63] studied the effect of short-term training after cardiac surgery for

valvular heart disease and coronary artery bypass graft surgery. As their training work rate, they used that at the *AT* rather than the level recommended by the American College of Sports Medicine,[6] which is 40% to 85% of the above-rest predicted maximum heart rate. They found the latter impractical both because of the range of recommended heart rate and also because most of the patients received β-adrenergic receptor blockade therapy, which limits the heart rate increase. Using peak $\dot{V}O_2$, *AT*, $\Delta\dot{V}O_2/\Delta WR$, and the time constant for the $\dot{V}O_2$ in response to constant work rate exercise as outcome measures, they found significant improvement in aerobic function in the group of postsurgery patients who underwent exercise training, but not in the control group of postsurgery patients who did not undergo exercise training.

Itoh and Kato[63] selected the work rate at the subject's *AT* because they regarded it as a safe yet effective work level for exercise training in these subjects. They reasoned that, at the *AT*, patients are able to supply the O_2 required to perform work because they do not endure a significant lactic acidosis and therefore the heart is not "overstressed." The sympathetic nervous system is not excessively stimulated at this work level, as evidenced by only minor changes in norepinephrine and epinephrine levels that take place at the *AT*, in contrast to the changes at higher work rates (see Chapter 2). Patients find this training program acceptable because they are able to maintain exercise at the *AT* over a prolonged period of time.

Using similar logic to Itoh and Kato,[63] Dubach et al.[40] examined the effect of a 2-month endurance exercise training program using a combination of walking and cycling training at a work rate comparable to that which would approximate the subject's *AT*. Training was started approximately 36 days after myocardial infarction. Myocardial injury, as evaluated by magnetic resonance imaging of the heart, was not extended by the training program. The trained patients increased peak $\dot{V}O_2$ and lactate threshold by 26% and 39%, respectively, whereas there was no detectable improvement in the nontrained control group.

Belardinelli et al.[17] studied the effect of exercise training on left ventricular diastolic filling in patients with dilated cardiomyopathy using pulsed Doppler echocardiography. They found that exercise training increased the *AT* and peak $\dot{V}O_2$ in these patients by improving the impairment of left ventricular relaxation. The basis of the increase in cardiac function was an improvement in peak early filling of the left ventricle.

The key physiological effect of training in the heart disease patient is the reduction in heart rate, thereby allowing more time for blood to flow through the coronary blood vessels and more time for cardiac filling. Also, because of more aerobic and less anaerobic regeneration of ATP after training, the lactic acidosis is less severe at a given level of exercise. Thus, there is less ventilatory drive and therefore less breathing stress. Finally, of great importance is a greater sense of well-being in patients as they find that they are becoming physically stronger and, as a consequence, more active.

Exercise Rehabilitation in Chronic Obstructive Pulmonary Disease

The National Emphysema Treatment Trial and other randomized trials support the concept that exercise training improves exercise tolerance and reduces dyspnea on exertion in patients with COPD undergoing rehabilitation.[113] CPET provides unequivocal evidence of the physiological benefits of training in these patients. Although most of the studies have been in patients with COPD, beneficial effects of exercise programs have also been published in patients with cystic fibrosis[94] and asthma.[34]

Patients with COPD are usually ventilatory limited; that is, their exercise tolerance is limited by the level of ventilation that they can attain and/or sustain. This occurs both because the level of ventilation that can be attained is low and because the level of ventilation required for a given level of exercise is high (see Fig. 5.6). The low ventilatory ceiling is related to the impaired lung mechanics and is manifest as a functionally zero breathing reserve (i.e., when ventilatory capacity is measured by the maximum voluntary ventilation maneuver or $FEV_1 \times 40$; see Fig. 5.9). Although we can predict that respiratory muscle fatigue is induced by the high work of breathing resulting from high expiratory airway resistance and hyperinflation-induced mechanical disadvantage of the diaphragm and chest wall muscles,[153] the evidence for this is not straightforward. The tidal volume usually does not get smaller and $\dot{V}E$ does not decrease as exercise is sustained. However, it is not unusual for $PaCO_2$ to increase as exercise work rate increases, providing evidence that alveolar ventilation cannot keep pace with the CO_2 load (see Case 49 in Chapter 10).

The high ventilatory requirement for a given level of exercise is dictated by inefficient gas exchange (high V_D/V_T), hypoxic and H^+ stimulation of ventilation, resulting from the production of CO_2 and lactate (see Fig. 5.5).[27,146] In some patients, lactic acidosis, at a low work rate as a result of detraining, is contributory to the increased ventilatory drive. But the detraining does not reduce the ability of the muscles to extract and utilize O_2 from the blood. Maltais et al.[74] showed that the muscles of patients with COPD are capable of extracting O_2 normally, suggesting that a primary muscle-bioenergetic defect is not limiting exercise tolerance in these patients. Also, the studies of Richardson et al.[109] demonstrate that if the ventilatory and cardiac requirements of exercise are reduced by exercising only one leg at a time, the exercising leg can increase its work capacity as compared with both legs performing the same exercise, simultaneously. These studies suggest that defects in the leg muscles do not limit exercise capacity in COPD.

Because, typically, patients with COPD are ventilatory limited, it is logical to turn our attention to modalities that can reduce their abnormal increases in ventilatory drive during exercise. For example, the onset of lactic acidosis at a low work rate, coupled with arterial hypoxemia and decreased oxygen delivery to the tissues (either due to increased pulmonary vascular resistance, decreased cardiac output as a result of the interference of lung mechanics on cardiac function,[24] or inefficient muscle perfusion), all might be expected to contribute to increase the ventilatory requirement above normal. Although some of these abnormalities are likely related to severe deconditioning due to inactivity,[27] a myopathy related to corticosteroid use might also be a factor.

Although it was doubted in the past that patients with COPD could gain physiological benefits from a program of exercise training,[19] it is now generally accepted as a useful therapeutic modality. New strategies—chief among them the use of exercise intensities that are a high percentage of peak exercise tolerance[112]—have demonstrated that physiological benefits *are* achievable. Thus, it is possible to decrease the exercise lactic acidosis by exercise training (Fig. 9.18), thereby reducing CO_2 and

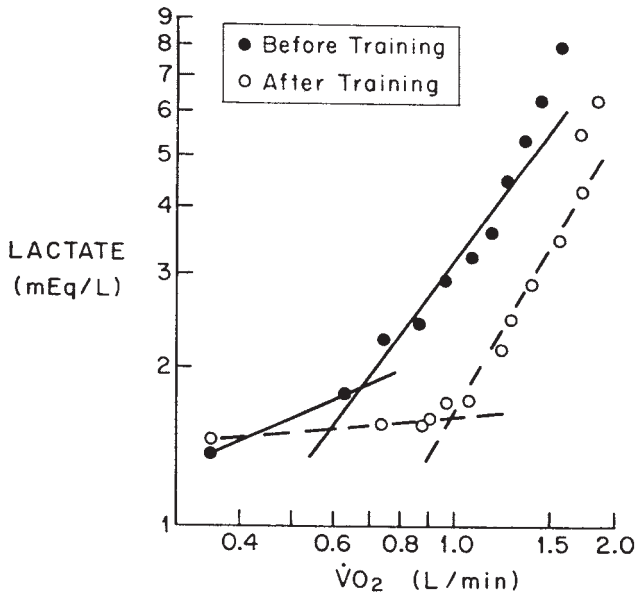

FIGURE 9.18. Blood lactate levels, before and after training, during increasing work rate exercise tests in a patient with chronic obstructive pulmonary disease undergoing rehabilitation. Arterial lactate is plotted versus oxygen uptake on a log-log scale. Closed circles are responses before training; open circles are responses after training. Before training, blood lactate rises very early in exercise. After training, blood lactate rise is delayed, and the lactate threshold (point of intersection of two line segments) occurs at a considerably higher $\dot{V}O_2$, indicating that a physiologic training response has occurred. (From Casaburi R, Patessio A, Ioli F, et al. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis.* 1991;143:9–18, with permission.)

H^+ production. CPET shows that exercise tolerance is increased after a rigorous program of rehabilitative exercise training in patients with COPD.[28] In a group of patients with predominantly moderate COPD, training-induced reductions in ventilatory requirement were closely correlated with the reduction in blood lactate levels (Fig. 9.19).[28] In a group of patients with more severe disease, the reduction in ventilatory requirement was associated with the adoption of a more efficient (slower, deeper) breathing pattern.[29]

Besides determining the degree (and mechanism) of improvement in exercise tolerance that occurs as a result of an exercise program, CPET has other well-defined uses in the context of pulmonary rehabilitation:

1. The contraindications to an exercise training program can be defined.
2. Exercise prescription guidelines for the patient can be developed.
3. The mechanism(s) of exercise limitation can be clarified.

A further modality to increase exercise tolerance might be O_2 breathing to provide O_2 during exercise to the patient with COPD, even if there is a small degree of arterial hypoxemia.[125] This maneuver might have four effects. First and most obvious, it inhibits the carotid bodies' responses to hypoxemia and H^+, thereby slowing breathing rate. Second, as a consequence of the slower breathing rate, it allows the patient with COPD to have more expiratory time and thereby exhale to a lower end-expiratory lung volume than during air breathing. Third, O_2 has some bronchodilator action. Fourth, it allows for washout of nitrogen from low-$\dot{V}_A/\dot{Q}$ areas of the lungs, thereby allowing end-expiratory lung volume to adjust downward because some of the O_2 replacing the N_2 will be absorbed.

ASSESSING THE EFFECTIVENESS OF TREATMENT

The major role of the heart, pulmonary and peripheral circulations, lungs, and ventilatory apparatus is to support the respiration of the cells and—specifically during exercise—the increased respiration of the skeletal muscles. Therefore, measurements of respiration in response to exercise should give the most direct global assessment of the function of these organ systems.

To use CPET for the purpose of evaluating therapy, however, it is necessary for the laboratory calibration to be accurate, to use sensitive end points, and to be consistent in methodology. Based on the experience of the multicenter Vasodilator Heart Failure Trials of the Veterans Affairs Hospitals, Cohn et al.[37] pointed out the need for well-trained technicians and careful calibration of the cardiopulmonary exercise system. Thus, it was of concern that some centers were performing CPET without a good understanding of what constituted a good or poor

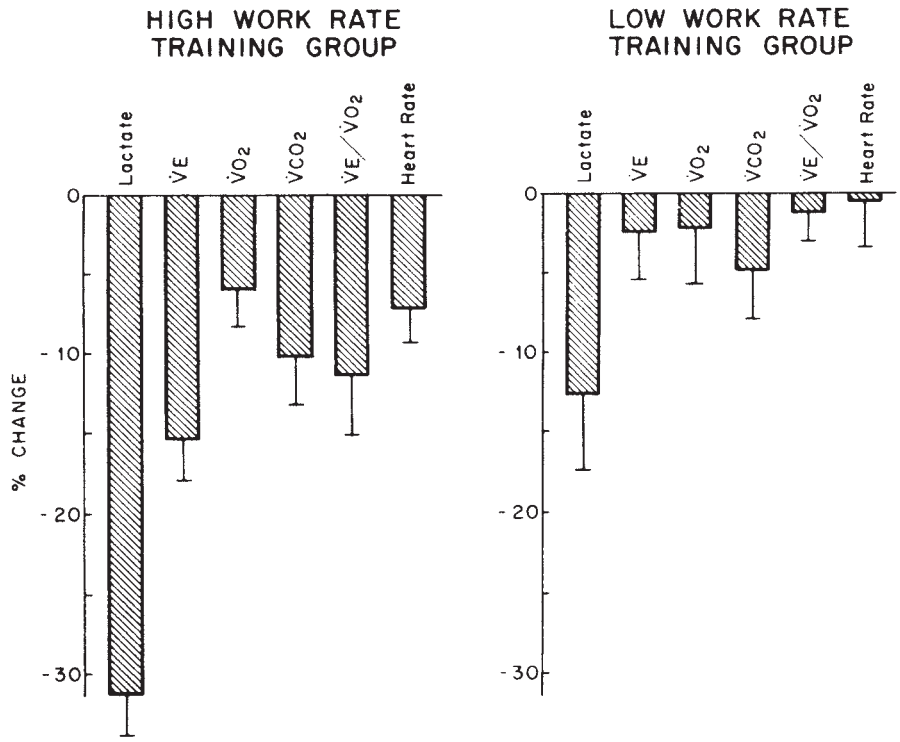

FIGURE 9.19. Changes in physiologic responses to an identical exercise task produced by two exercise training strategies in patients with chronic obstructive pulmonary disease. **Left:** High work rate training group (n = 11). **Right:** Low work rate training group (n = 8). Note that patients performed the same total work in their training program irrespective of group assignment. Percent change is calculated from the average change in response at the time the pretraining study ended. Vertical lines represent 1 standard error of mean. Decreases in blood lactate, ventilation, O_2 uptake, CO_2 output, ventilatory equivalent for O_2, and heart rate are observed for both training regimens, but decreases are appreciably greater for the high work rate training group. (From Casaburi R, Patessio A, Ioli F, et al. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis.* 1991;143:9–18, with permission.)

test. Several centers produced results in which tests of normal subjects (controls) yielded $\Delta\dot{V}O_2/\Delta WR$ values that were either too low or too high to be physiological—that is, they were considerably outside of the normal range (see Chapter 2). Eventually, the normal control subjects at all centers had appropriate values for $\Delta\dot{V}O_2/\Delta WR$, thereby increasing confidence in the data from the sites. If the leaders at these centers had been trained in cardiopulmonary exercise physiology, they would have recognized immediately that their results were incorrect, rather than recognizing the problem only when experts reviewed the collected data. By knowing that $\Delta\dot{V}O_2/\Delta WR$ should be approximately 10 mL/min/W in all normal subjects for any increasing work rate cycle ergometer exercise test protocol, one is provided with an internal calibration for a laboratory and an ability to detect gross errors early in a study.

Figure 4.2 and the cases in Chapter 10 show the consistency of the value of $\Delta\dot{V}O_2/\Delta WR$ in all normal subjects. We obtain the same exercise gas exchange measurements when studying the same subject in any of our three hospital laboratories. All give the same results despite different equipment because of the use of trained technicians and the calibration procedures described in Chapter 6. Accuracy is further validated by use of a metabolic simulator.[62]

The physiological responses to exercise are reproducible in patients with relatively stable pathophysiology. Hansen et al.[52] studied patient performance reproducibility and reader reproducibility in 114 paired tests performed 1 to 3 days apart in 42 exercise-limited patients with PAH. Patient performance reproducibility rates were 5.8%, 6.5%, and 3.3%, and the reader reproducibility rates were 0.6%, 8.5%, and 2.1% for peak $\dot{V}O_2$, *AT*, and $\dot{V}E/\dot{V}CO_2$ at the *AT*, respectively.

Evidence for the value of CPET for assessment of treatment is further provided by the case shown in Figure 9.10. This figure illustrates the wealth of information obtained from both a single exercise test and sequential exercise testing to evaluate the efficacy of epoprostenol treatment in PAH. These studies demonstrate that, at the outset of therapy, the patient was totally and critically incapacitated, despite being willing to do cycle ergometry to her best ability. Fortunately, she had some response to therapy by 4 months (test 2). At 8 months (test 3), based on further improved perfusion to ventilated lung (reduction in $\dot{V}E/\dot{V}CO_2$ at the *AT*, and slope of $\dot{V}E$ versus $\dot{V}CO_2$ and increased O_2 transport (increase in peak $\dot{V}O_2$, *AT*, and O_2 pulse) during exercise, she was taken off the lung transplantation list. She had no further functional gain past test 5 (16 months) and remained at the same level of function for greater than 12 years, the limit of observation. Thus, she was left with an abnormally low peak $\dot{V}O_2$ and O_2 pulse (60% and 70% of predicted, respectively) and high $\dot{V}E/\dot{V}CO_2$ at the *AT* (third panel down, Fig. 9.10), but at a level of function that was adequate to pursue most forms of physical activity and her motherly duties. These objective assessments allowed her and her physicians to understand her functional disability and capacity much better than without the cardiopulmonary exercise tests.

Several other cases are presented in Chapter 10 in which sequential studies documented that therapy

improved function (Cases 13, 42, 58, and 77) and several in which therapy did not improve function, significantly (Cases 40, 50, and 56). Importantly, the cardiopulmonary exercise tests provide the physician with reproducible and objective information needed to evaluate the clinical course of the patient and the effectiveness of therapeutic interventions.

SCREENING FOR DEVELOPMENT OF DISEASE IN HIGH-RISK PATIENTS

The intimate relationship between O_2 transport and exercise bioenergetics is clear. The normal gas exchange response to exercise is also well defined. Abnormal gas exchange responses to exercise are characteristic for disease in a specific organ system. Thus, to detect disease of impaired coupling of external to cellular respiration at an early stage—and possibly prevent serious progression of the illness—a noninvasive cardiopulmonary exercise test is probably the most sensitive, most comprehensive, and most cost-effective single test available to patients and physicians at this time.

Few investigative studies have been done that take advantage of noninvasive CPET to detect developing disease of the heart, lungs, pulmonary, or systemic circulations, or the muscles. A normal peak $\dot{V}O_2$, *AT*, and $\Delta\dot{V}O_2/\Delta WR$ in response to exercise are required for an individual to function normally. Because these measurements will become abnormal with any functional impairment of the organs coupling pulmonary to cellular respiration, sequential CPET would be expected to be sensitively affected with a developing defect in the coupling. For example, the physician can use CPET measurements to detect deterioration of cardiovascular function with time, such as illustrated by Cases 9, 19, and 20 in Chapter 10. Thus, periodic cardiopulmonary exercise tests measuring $\dot{V}O_2$, *AT*, and $\Delta\dot{V}O_2/\Delta WR$ might be important to perform in people with strong family histories of CAD, including silent myocardial ischemia. Similarly, the measurement of the slope of $\dot{V}E$ versus $\dot{V}CO_2$ and $\dot{V}E/\dot{V}CO_2$ at the *AT*, in view of the uniform predicted values of these measurements, would likely be sensitive noninvasive methods to detect the development of pulmonary vascular disease in patients such as those susceptible to thromboembolic disease and the pulmonary vasculopathy that leads to primary pulmonary hypertension or pulmonary hypertension with connective tissue diseases.[41]

GRADED EXERCISE TESTING AND THE ATHLETE

Training for athletic competition, especially of the endurance kind, owes as much to the accumulated lore of the practices of previously successful athletes as to the application of training strategies based on the results of physiological experimentation. The underlying theme of the various approaches to endurance training, however, is that of stressing the system during training beyond the demands of the actual event. How far beyond the power demands of the event and with what patterns of work–rest repetition remain the central issues.

Although many approaches will improve performance, the challenge is to determine the optimum pattern: the one that will achieve the greatest improvement in the available time. Laboratory exercise testing of the graded or incremental kind can provide a basis for establishing such a strategy, ensuring that the chosen strategy is successfully accomplished during the training session, and establishing objective criteria to support the physiological benefits of the training scheme.

This is most clearly evident in considering the extremes of event duration: sprints and marathons (and beyond). It is hard to see how knowledge of a subject's $\dot{V}O_2$max, critical power, and *AT* can possibly influence the choice of training speeds for a sprinter. Considerations of the recovery kinetics of, for example, muscle or blood lactate (which, for the purposes of this discussion, we will use as proxy variables for the fatigue-inducing mechanisms) might be beneficial to the choice of interval strategy in the future. Indices of peak and mean power over a short maximum-effort sprint, such as provided by the Wingate test,[14] offer more in this regard. For example, if these indices show improvement as a result of the training program but performance at the event does not, this would suggest that the athlete's technique should be the focus of attention.

For events of marathon duration or longer, the glycogen-squandering aspects of anaerobic glycolysis and consequent increased rate of lactate production are detrimental to performance. Consequently, a knowledge of the athlete's speed at the *AT*, by an appropriate measurement or estimation technique (including perceptual correlates[25]) can serve both as a means of optimizing the rate at which the event is actually performed[158] and as a frame of reference for a strategy for training at some higher speed that will induce a given degree of lactic acidemia—that is, one that is sustained at some target value aimed at inducing a training effect (in this case, to increase the *AT* and hence the potential optimum performance rate).

At the intervening middle distances, knowledge of the subject's profile of aerobic function is likely to be of considerably greater importance. Although Newsholme and Castell[86] have suggested that muscle glycogen depletion can contribute to fatigue at running events as short as 10,000 meters, it is likely that in these events fatigue is a result of metabolites increasing inexorably locally within muscle[121] and/or in sites within the brain[86] at a rate that causes them to attain a maximal, and limiting, value at the end of the race.

The upper limit of the work rate at which both $\dot{V}O_2$ and blood lactate can be maintained at a high but constant level has been defined[104] to be, in general terms, the subject's critical power.[55] In healthy young subjects, this occurs on average at a $\dot{V}O_2$ of approximately 50% of the difference between the *AT* and the peak $\dot{V}O_2$ and at a blood lactate level of approximately 4 to 5 mM. Presumably, this is the power output at which the rate of muscle lactate production is balanced by the rate of lactate consumed by other tissues and particularly by the liver (Cori cycle). However, these levels vary among subjects; hence, it is important to determine the specific level for a given subject rather than relying on a group-mean value to guide training. These profiles will establish whether the training intensity is sufficiently high for the training target and also serve to monitor training-induced improvements. However, it is important to recognize that a particular level of blood lactate can be at resting levels or attained at either by a relatively low constant-load exercise bout[147] or by work–recovery repetitions involving appreciably greater work rates.[11,143] This allows the recruitment pattern of muscle fibers and the metabolic and acid–base consequences of work to be proportionally manipulated for the training purpose.

Overtraining is also important to the athlete because it can lead to increased risk of infections and depressed immunologic function, in addition to decrements of performance.[58] This appears to be a manifestation of prolonged high-intensity training; lower levels can boost immune function. The use of graded exercise testing to establish the upper level of beneficial training intensities and duration should provide insight into the deleterious aspects of inappropriate training.

As more is learned about the physiological mechanisms that trigger "training effects" and how the variables of intensity, duration, and recovery interact to induce the effects,[13] laboratory testing will become even more useful in training prescriptions.

SUMMARY

Until the 1980s, CPET had not been applied in a general way in medicine because of the apparent complexity and time demands of the methods required to obtain the useful data. However, with the advent of automated gas analyzers, sensitive measuring devices, and computerized methods to calculate and display the massive amount of useful data that can be obtained from cardiopulmonary exercise tests, it is being recognized as an accurate, noninvasive technology with widespread applications at relatively low cost. We have used it most effectively for differential diagnosis, including unique diagnoses that cannot be made objectively without CPET. It takes the guesswork and bias out of differential diagnosis and effectiveness of therapy. It also makes impairment evaluation for disability more objective. It has been a very helpful guide in both cardiac and pulmonary rehabilitation for determining both the training work rate and whether improvement in exercise performance has occurred. In recent years, CPET has been shown to be a more accurate predictor of severity of disease and predictor of survival time in patients with heart failure than other techniques currently used by cardiologists for grading severity of chronic heart failure. Thus, it is now used to prioritize patients for heart transplantation, with the predicted insights from the measured peak $\dot{V}O_2$ overriding other cardiologic measurements. It is likely that these same guidelines can be applied to lung transplantation in patients with primary pulmonary hypertension and lung reduction surgery in patients with emphysema.

CPET has obvious applications in determining the therapeutic effectiveness of drugs and procedures. Less well documented, but obvious in application, is the use of this quantitative approach to detect disease early in its development—that is, before it is so advanced that abnormalities develop at rest and before they are reversible. The increasing number of applications for which CPET is currently employed attests to the growing recognition of its importance in medicine. It provides the potential to reduce health care costs by streamlining the diagnostic approach to disease and facilitating treatment decisions.

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CHAPTER

10

Case Presentations

In this chapter, case examples are presented along with discussion of the data and their interpretation. The cases were selected to illustrate the range of normal cardiovascular and ventilatory responses during cardiopulmonary exercise testing and how these are affected by chronic diseases that cause exercise intolerance. A pathologic defect in any component of the coupling of external-to-cellular respiration might impair exercise performance, but the type of gas exchange abnormality that results, usually allows identification of the organ system defect of greatest significance.

Although exercise gas exchange responses of normal children were discussed in Chapter 7, all of the cases presented in this chapter are with adults, reflecting the clinical training and practice of our faculty. The cases do not necessarily show ideal data from uniformly cooperative subjects or represent the sole findings of a particular clinical condition. In fact, because these studies come from real patients, they include some in which patient performance was less than optimal or the data, though we believe accurate, are not particularly pretty.

A central goal of this chapter is to offer a systematic approach to interpretation of exercise data. Many of the cases are therefore discussed in the context of the flowcharts presented in Chapter 8. Even for cases in which patients' diagnoses were known prior to testing, the flowchart analysis serves to reinforce characteristic patterns of findings of different categories of disease. Other cases are discussed without reference to the flowcharts, reflecting the personal approaches of the authors contributing to the cases or the specific purpose for the test.

The general format of the data for each case is similar. A brief clinical history is provided, limited to information needed to appreciate the context of the test and interpret the results. Pertinent demographic information and resting pulmonary function data are shown in the first table for each case, and a summary of key variables or parameters from the exercise data is given in the second table. A third (and for some cases, fourth if more than one test was performed) table is presented with exercise data displayed as 30-second averages of breath-by-breath measurements from rest through recovery. For consistency of presentation, 30-second averages are used both in this table and in the figures accompanying each test, which are in the form of nine-panel graphical displays.

The nine-panel figures are organized as described in Chapter 4. A number of formatting conventions are observed to facilitate data interpretation. The predicted value for peak $\dot{V}O_2$ is shown on the panel 1 graph, and for both peak $\dot{V}O_2$ and peak heart rate on the panel 3 graph. For cycle ergometry tests, work rate is plotted on panel 1 and scaled on the right *y*-axis such that each 100 W corresponds to 1 L of $\dot{V}O_2$ on the left *y*-axis. This results in the $\dot{V}O_2$ and work rate data increasing in parallel on the graph if their relationship ($\Delta\dot{V}O_2/\Delta WR$) is normal (10 mL $\dot{V}O_2$ per watt^{-min}), which facilitates identification of deviations from normal. The relationship of $\dot{V}CO_2$ as a function of $\dot{V}O_2$ (V-slope) is plotted in panel 3 with equal scaling on the *x*- and *y*-axes, and a dashed line is provided on the plot that identifies the slope of 45 degrees. This facilitates identification of the anaerobic threshold as the $\dot{V}O_2$ above which $\dot{V}CO_2$ increases with a slope steeper than that of the dashed line. When arterial blood gases are available, they are included in third table and the gas tensions are plotted in panel 7 of the nine-panel figure. Predicted values shown on the graphs and in the second table of each case are the mean values (for the anaerobic threshold, the lower limit of normal) taken from reference equations discussed in Chapter 7. The case interpretations take into consideration the range of normal values within healthy populations and the appropriateness of the reference values to the patient being tested.

The various components of the case presentation are each important to the interpretation. For example, although the second table of each case summarizes many key findings, there are other pertinent data needed for interpretation that are only appreciated by review of the graphical data. These include the pattern and value of R over the course of exercise in panel 8 of the nine-panel graph, which reflects the effect of lactic acidosis on the rate of $\dot{V}CO_2$ relative to $\dot{V}O_2$, which is often referenced as evidence of the extent of exercise above the anaerobic threshold and thus the adequacy of effort. Similarly, the pattern of increase of heart rate relative to $\dot{V}O_2$, shown in panel 3, is helpful in identifying whether a low peak heart rate was due to premature termination

of the test or due to a blunted heart rate response across the range of exercise. Additional results, such as electrocardiogram (ECG) findings and the patient's subjective symptoms, are found in the narrative summary of the test. Case interpretation involves integrative and iterative review of these numerical, graphical, and narrative data.

The print version of this book includes 80 cases. An additional 30 cases are included in the online materials. There are undoubtedly many clinical disorders that are not represented among them, but practical considerations limit the number that can be included. However, it is hoped that with consideration of the interaction of physiologic mechanisms during exercise that determine normal cardiorespiratory responses and with the physiologic concepts developed in these cases, the reader will be able to recognize pathophysiologic responses that are not presented.

These first 80 cases are organized in groups, beginning with normal tests, followed by tests reflecting various diseases, then examples of patients with mixed diseases, and finally, cases illustrating specific applications of exercise testing. Additional cases in the online version of this text are not presented in a particular order but represent additional examples of tests conducted for a variety of indications. Presentation of the 80 print cases follows.

NORMAL

Cases 1 to 11 illustrate the range of normal exercise responses. These include studies of apparently healthy adults of both genders and various ages and levels of fitness. Among these are paired tests that illustrate the effects of selected conditions or circumstances, including O_2 breathing, β-adrenergic blockade, aging, and cigarette smoking, on the test results of normal individuals.

CHRONIC HEART FAILURE

Cases 12 to 15 are patients with chronic left ventricular systolic heart failure. The patients were studied while their heart failure was compensated on treatment, which was considered standard care at the time of their testing.

MYOCARDIAL ISCHEMIA

Cases 16 to 20 illustrate how exercise-induced myocardial ischemia may be manifested in exercise gas exchange variables.

OTHER CARDIOVASCULAR DISEASES

A number of other diverse cardiovascular conditions are represented in Cases 21 to 34. These include peripheral arterial disease in Cases 21 and 22, impairment due to disturbances of cardiac rate or rhythm in Cases 23 through 25, and a variety of congenital and structural heart diseases in Cases 26 through 32. Cases 33 and 34 are grouped with the cardiovascular disorders because they appeared to be limited by circulatory capacity, perhaps due to impaired central circulatory filling. The unusually extensive testing that they underwent allows comparison of noninvasive gas exchange measurements to central hemodynamic and arterial, muscle venous, and central venous blood gas changes during exercise.

PULMONARY VASCULAR DISEASES

Cases 35 to 44 are all examples of pulmonary vascular disorders. Cases 35 to 38 are patients with primary or idiopathic pulmonary arterial hypertension, Cases 39 to 41 are patients with secondary pulmonary vascular disease associated with collagen vascular disorders, and Cases 42 to 44 represent other pulmonary vascular defects.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Cases 45 to 52 are patients with varying severity of chronic obstructive pulmonary disease.

INTERSTITIAL LUNG DISEASES

Cases 53 to 59 are patients with mild-to-severe parenchymal lung diseases. The pathophysiology reflected in the more severe cases is similar to that of the patients categorized as having pulmonary vascular disease secondary to collagen vascular disorders.

EXTRAPULMONARY RESTRICTION

Cases 60 to 62 illustrate the effects of restricted ventilation due to extrapulmonary processes on exercise function.

MUSCLE DISORDERS

Cases 63 to 66 are patients with exercise limitations due to skeletal muscle myopathies. Although many muscle disorders impair exercise because of altered motor function, the cases presented here are disorders of the metabolic processes involved in energy production in the muscle. These are the kinds of muscle disorders most likely to be referred to an exercise laboratory with symptoms of exertional dyspnea or fatigue.

MIXED DISORDERS

Each of the patients presented in Cases 67 to 73 had a combination of two or more conditions that could independently or interactively limit exercise. These conditions include chronic heart, lung, and peripheral arterial diseases; obesity; hypertension; and anemia. In our experience, most patients referred for clinical testing have more than one medical problem, and a great many of the other cases in this chapter could have been included in this section. An important application of cardiopulmonary exercise testing is to help discern the contributions of comorbid conditions to the patient's symptoms. The cases presented here are discussed with a particular focus on the interaction of coexisting conditions or diseases on exercise function.

APPLICATIONS OF EXERCISE TESTING

Cases 74 to 80 were selected to illustrate specific applications of exercise testing. Each of these could have been included in one or more of the earlier groupings described previously. Similarly, virtually all of the other cases in this chapter illustrate one or more applications of exercise testing. The discussion of these cases directs attention to these applications and illustrates how data from the test may be used in clinical decision making. Case 74 is an example of exercise testing for grading the severity of the disease and estimating prognosis of a patient with chronic systolic heart failure. Case 75 also illustrates the use of exercise testing for gauging prognosis, in this case in the preoperative evaluation of a patient with lung cancer. Case 76 is an example of exercise testing for evaluating work fitness or disability. Case 77 illustrates the use of exercise testing prior to exercise training of a patient with chronic obstructive pulmonary disease entering pulmonary rehabilitation. A post-rehabilitation test further illustrates the basis for improvement in function following exercise training. Cases 78 to 80 were chosen as examples of exercise testing for the evaluation of unexplained dyspnea. The first, Case 78, is an example in which exercise testing established a specific diagnosis. Case 79 is a case in which exercise testing narrowed the differential diagnosis and directed further diagnostic testing needed for definitive diagnosis of the cause of dyspnea. Finally, Case 80 is an illustration of how a negative, or normal, test can be helpful in clinical decision making by allowing the treating physicians to limit further, more invasive testing.

PHYSIOLOGICAL INTERPRETATIONS FROM CASE DISCUSSIONS

The case discussions draw on the information in each of the prior chapters of this book. Beginning with an appreciation of the normal cardiorespiratory and metabolic responses to exercise, patients' maximal and submaximal exercise data can be characterized by a set of parameters for comparison with reference values and interpretation in the context of clinical history. It should be clear from the range of findings in these cases that the effect of a particular disease on patients' exercise functions is not invariant. Factors such as disease severity, compensatory adaptations, comorbid conditions, habitual activity level, and medications can modify how the disease impacts exercise function. This is part of the reason that measurements of a single organ function at rest are poor predictors of the effect of disease on functional capacity. We hope that the principles presented in the earlier chapters provide the reader with the necessary background to interpret the pathophysiology of exercise intolerance in individual patients.

PRINCIPLES OF INTERPRETATION: A FLOWCHART APPROACH

Throughout this chapter, the flowchart approach, described in Chapter 8 of this monograph, is used in the discussion of cases. In the analysis section of most cases, reference is made to identifying relevant flowcharts and following the numbered branch points through the charts, to categorize the exercise findings in terms of clinical diagnoses. With time, this systematic approach to interpreting the test data becomes intuitive because the flowcharts have a physiological basis. Patterns of abnormalities and the differential diagnosis of processes associated with them become familiar, and step-by-step referral to flowcharts becomes unnecessary.

SYMBOLS AND ABBREVIATIONS

The symbols and abbreviations used in the case presentations and tables reflect standard usage in medical journals and prior sections of this book. For readers unfamiliar with them, symbols and abbreviations are identified in Appendix A, and their meanings defined in Appendix B, the Glossary. Formulas used for deriving values for calculated variables are presented in Appendix C, Calculations, Formulas, and Examples.

Case 1 Normal Man

CLINICAL FINDINGS

A 55-year-old executive was referred for exercise testing after complaining of decreased exercise tolerance. He noted weakness, fatigue, and some dyspnea after jogging one block, but he could walk 3 miles on a level surface without difficulty. He had become symptomatic after a period of inactivity due to an ankle injury 2 years earlier and felt he never returned to his former exercise tolerance. He did not report chest pain, syncope, palpitations, coughing, or wheezing. He had smoked half a pack of cigarettes per day for 10 years but had reduced his smoking to three to four cigarettes per week. He took no medications. Physical examination, chest roentgenograms, and resting electrocardiogram (ECG) were normal. Demographic and clinical data are summarized in Tables 10.1.1 and 10.1.2. For this and all following cases, the data are presented using standard abbreviations and symbols as defined in Appendices A, B, and C of this book.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes, then the work rate was increased 20 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of thigh fatigue. Twelve-lead ECG recordings remained normal during exercise.

Table 10.1.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		55
Sex		Male
Height (cm)		182
Weight (kg)	83	80
Hematocrit (%)		41
VC (L)	4.75	6.06
IC (L)	3.17	4.16
TLC (L)	7.08	8.24
FEV_1 (L)	3.76	4.52
FEV_1/VC (%)	79	75
MVV (L/min)	151	200
D_{LCO} (mL/mm Hg/min)	28.8	28.30

INTERPRETATION

Comments

The results of the respiratory function studies are within normal limits (Table 10.1.1).

Analysis

Referring to the data in Table 10.1.2 and Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and anaerobic threshold are normal. Referring to Flowchart 2 (Fig. 8.2), the ECG and arterial blood gases (Table 10.1.3) are normal throughout exercise; the O_2 pulse at the maximum work rate is normal.

Conclusion

This man has normal exercise function. His complaints could reflect anxiety regarding his physical status and residual deconditioning after a period of inactivity.

Table 10.1.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.47	2.53
Maximum heart rate (beats/min)	165	176
Maximum O_2 pulse (mL/beat)	15.0	14.5
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	9.8
AT (L/min)	>1.07	1.2
Blood pressure (mm Hg [rest, max])		144/81, 225/87
Maximum $\dot{V}E$ (L/min)		107
Exercise breathing reserve (L/min)	>15	93
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.2	25.7
PaO_2 (mm Hg [rest, max ex])		98, 110
$P(A-a)O_2$ (mm Hg [rest, max ex])		5, 15
$PaCO_2$ (mm Hg [rest, max ex])		39, 32
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		0, –5
V_D/V_T (rest, heavy ex)		0.26, 0.15
HCO_3^- (mEq/L [rest, 2-min recov])		25, 12

Table 10.1.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	PO_2, mm Hg			PCO_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	153/87								7.42	25		97			39				
0.5	Rest		74	14	12.2	0.32	0.34	4.6	0.94			112			35			34	32	
1.0	Rest		78	13	9.8	0.25	0.31	4.0	0.81			105			38			35	28	
1.5	Rest		78	13	9.9	0.26	0.32	4.1	0.81			105			37			34	27	
2.0	Rest	144/81	80	11	9.2	0.26	0.34	4.3	0.76	7.42	24	103	98	5	38	38	0	32	24	0.26
2.5	Rest		79	12	11.4	0.32	0.42	5.3	0.76			102			38			32	25	
3.0	Rest		76	10	13.2	0.38	0.43	5.7	0.88			106			37			33	29	
3.5	Unloaded		93	16	18.2	0.56	0.66	7.1	0.85			105			38			30	26	
4.0	Unloaded		91	12	17.1	0.58	0.69	7.6	0.84			104			38			28	23	
4.5	Unloaded		87	19	16.2	0.48	0.57	6.6	0.84			104			40			30	26	
5.0	Unloaded		83	19	14.5	0.42	0.53	6.4	0.79			103			39			31	24	
5.5	Unloaded		85	22	16.9	0.48	0.59	6.9	0.81			102			40			31	25	
6.0	Unloaded	171/87	85	25	16.4	0.50	0.62	7.3	0.81	7.41	25	101	100	2	40	40	0	29	23	0.21
6.5	20		84	24	19.7	0.65	0.80	9.5	0.81			100			41			27	22	
7.0	20		86	28	18.1	0.58	0.67	7.8	0.87			104			40			27	23	
7.5	40		92	23	21.6	0.73	0.87	9.5	0.84			99			43			27	23	
8.0	40	183/84	93	18	19.9	0.69	0.82	8.8	0.84	7.40	24	101	99	5	42	40	–2	27	22	0.18
8.5	60		101	17	26.7	0.92	1.06	10.5	0.87			101			41			27	24	
9.0	60		104	17	26.0	0.91	1.03	9.9	0.88			102			42			27	24	
9.5	80		108	16	25.8	0.93	1.03	9.5	0.90			100			44			26	24	
10.0	80	195/81	110	16	28.4	1.07	1.16	10.5	0.92	7.38	23	103	98	9	43	40	–3	25	23	0.14
10.5	100		116	16	37.3	1.38	1.37	11.8	1.01			107			41			26	26	
11.0	100		123	17	38.1	1.44	1.41	11.5	1.02			107			43			25	26	
11.5	120		131	18	42.0	1.54	1.45	11.1	1.06			106			43			26	28	
12.0	120	207/87	135	19	44.5	1.67	1.62	12.0	1.03	7.37	23	107	103	7	43	41	–2	26	26	0.17
12.5	140		142	18	49.4	1.83	1.67	11.8	1.10			108			43			26	29	
13.0	140		146	20	49.4	1.87	1.74	11.9	1.07			109			42			26	27	
13.5	160		152	20	55.5	2.09	1.88	12.4	1.11			110			42			26	29	
14.0	160	213/90	155	19	58.3	2.23	1.99	12.8	1.12	7.35	21	110	101	13	42	39	–3	25	28	0.13
14.5	180		160	20	67.7	2.51	2.18	13.6	1.15			106			45			26	30	
15.0	180		163	22	69.5	2.55	2.16	13.3	1.18			112			42			27	31	
15.5	200		167	24	77.3	2.74	2.26	13.5	1.21			112			42			27	33	
16.0	200	225/87	170	27	90.7	3.10	2.42	14.2	1.28	7.31	18	115	105	15	40	36	–4	29	37	0.16
16.5	220		174	31	107.2	3.40	2.53	14.5	1.34			119			37			31	41	
17.0	220	216/90	176	30	102.9	3.20	2.36	13.4	1.36	7.30	15	118	110	15	37	32	–5	31	43	0.14
17.5	Recovery		162	24	84.3	2.64	1.93	11.9	1.37			114			41			31	43	
18.0	Recovery		158	21	71.5	2.10	1.26	8.0	1.67			124			35			33	55	
18.5	Recovery		151	18	57.6	1.67	1.02	6.8	1.64			126			34			34	55	
19.0	Recovery	165/75	149	19	52.7	1.44	0.91	6.1	1.58	7.22	12	126	124	5	32	30	–2	35	56	0.18

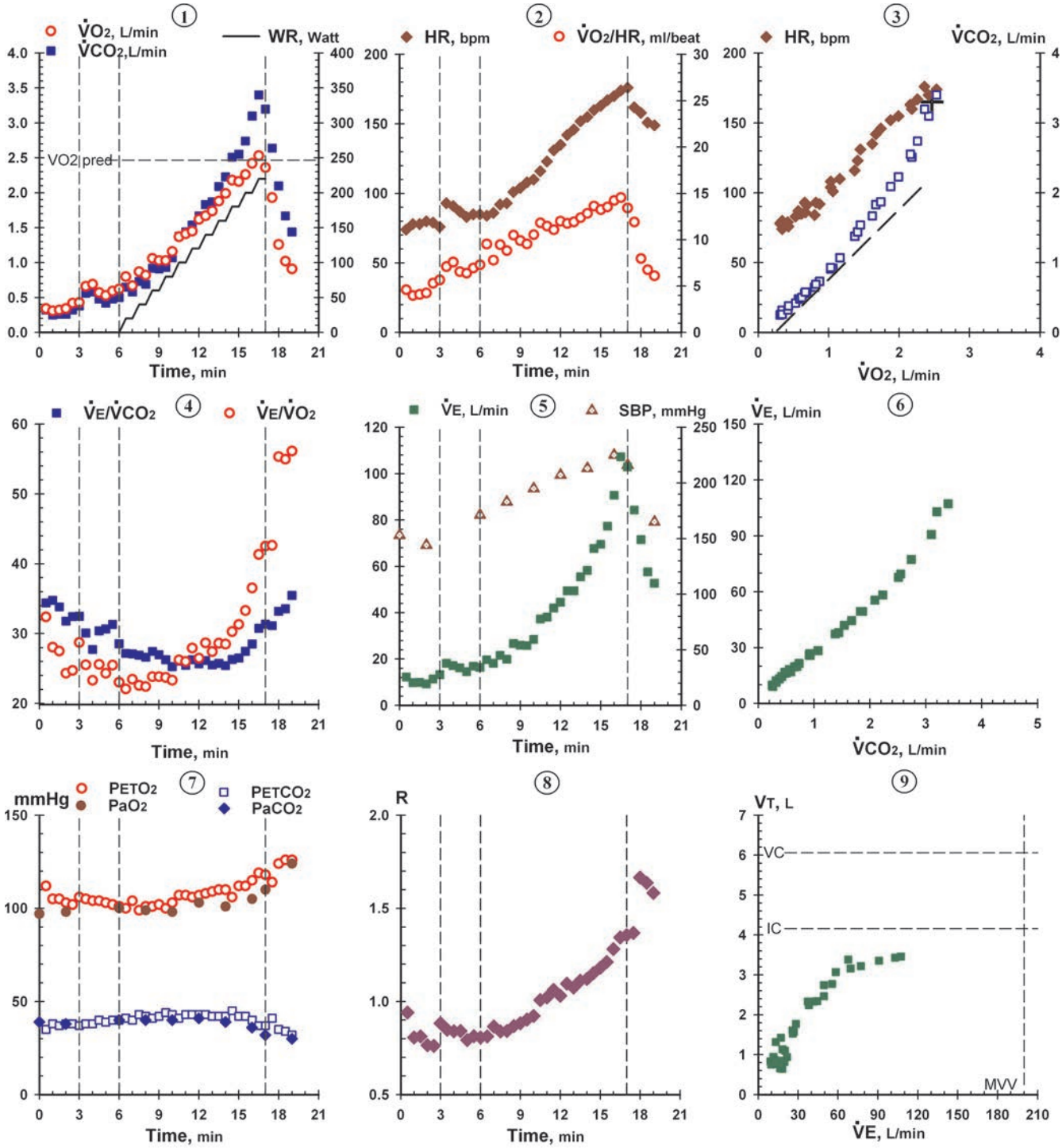

FIGURE 10.1.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 2 Normal Athletic Man

CLINICAL FINDINGS

A 31-year-old physiologist is a frequent marathon runner. He has no known health problems and trains several times weekly.

EXERCISE FINDINGS

The subject performed exercise on a cycle ergometer. He pedaled without added load at 60 rpm for 2 minutes. The work rate was then increased 30 W every minute to his symptom-limited maximum. There were no arrhythmias, and the ECG remained normal (Tables 10.2.1, 10.2.2, and 10.2.3).

INTERPRETATION

Comments

This case is presented to illustrate the results of a normal, athletic subject.

Analysis

The results of this study demonstrate how cardiovascular fitness is reflected in the responses to exercise compared to the responses of sedentary individuals. Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and the anaerobic threshold are considerably above the predicted values (Table 10.2.2), which were derived from a sedentary population. The exceptionally high O_2 pulse at maximum work rate reflects the large stroke volume that this subject must have. Assuming that the mixed venous O_2 saturation was as low as 20%, the peak O_2 pulse of 28.3 mL/beat would indicate that the subject's exercise stroke volume must be approximately 175 mL. The normal ventilatory equivalents for O_2 and CO_2 at the anaerobic threshold (panel 4 in Fig. 10.2.1) reflect the ventilation–perfusion matching of a normal subject and are quite similar to those of the more sedentary but healthy man presented in Case 1. The maximum exercise ventilation, however, approximates the patient's maximum voluntary ventilation (MVV), so that the breathing reserve is essentially zero. Ventilatory limitation is a common finding in exceptionally fit people whose cardiovascular capacity has been increased by virtue of training.

Conclusion

This is an exceptionally fit, normal subject.

Table 10.2.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		31
Sex		Male
Height (cm)		182
Weight (kg)	83	81
Hematocrit (%)		43
VC (L)	5.48	6.27
IC (L)	3.65	3.56
FEV_1 (L)	4.43	4.51
FEV_1/VC (%)	81	72
MVV (L/min)	182	185

Table 10.2.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	3.22	4.95
Maximum heart rate (beats/min)	189	175
Maximum O_2 pulse (mL/beat)	17.0	28.3
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	11.5
AT (L/min)	>1.32	2.5
Maximum $\dot{V}E$ (L/min)		186
Exercise breathing reserve (L/min)	>15	–1
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	24.7	25.8

Table 10.2.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest		77	25	13.7	0.30	0.45	5.8	0.67			103			33			39	26	
1.0	Rest		74	31	17.0	0 35	0.52	7.0	0.67			94			36			41	28	
1.5	Rest		62	17	14.1	0.32	0.45	7.3	0.71			101			34			40	28	
2.0	Rest		68	10	14.5	0.33	0.41	6.0	0.80			112			30			41	33	
2.5	Unloaded		66	27	13.0	0.28	0.46	7.0	0.61			88			39			38	23	
3.0	Unloaded		76	25	20.4	0.53	0.82	10.8	0.65			94			37			34	22	
3.5	Unloaded		75	23	18.9	0.48	0.71	9.5	0.68			97			36			35	24	
4.0	Unloaded		64	26	15.7	0.39	0.60	9.4	0.65			93			39			35	22	
4.5	30		77	18	16.3	0.46	0.71	9.2	0.65			94			39			32	21	
5.0	30		76	25	20.1	0.52	0.77	10.1	0.68			96			38			35	23	
5.5	60		84	26	23.3	0.64	0.94	11.2	0.68			92			39			33	22	
6.0	60		85	27	23.8	0.69	1.01	11.9	0.68			93			40			31	21	
6.5	90		90	28	28.7	0.89	1.26	14.0	0.71			94			40			30	21	
7.0	90		94	24	29.6	0.99	1.37	14.6	0.72			92			42			28	20	
7.5	120		100	21	32.2	1.16	1.54	15.4	0.75			94			42			26	20	
8.0	120		101	22	36.5	1.31	1.65	16.3	0.79			97			42			26	21	
8.5	150		105	26	41.9	1.41	1.72	16.4	0.82			95			43			28	23	
9.0	150		106	25	43.1	1.50	1.85	17.5	0.81			93			44			27	22	
9.5	180		114	27	50.6	1.84	2.17	19.0	0.85			95			44			26	22	
10.0	180		117	25	53.2	2.03	2.39	20.4	0.85			92			46			25	21	
10.5	210		124	27	59.3	2.19	2.40	19.4	0.91			96			46			26	24	
11.0	210		127	30	71.7	2.61	2.79	22.0	0.94			96			46			26	25	
11.5	240		130	30	75.0	2.73	2.83	21.8	0.96			105			41			27	26	
12.0	240		135	31	80.6	2.97	3.05	22.6	0.97			105			41			26	26	
12.5	270		140	30	78.9	3.06	3.22	23.0	0.95			97			47			25	24	
13.0	270		142	32	85.0	3.27	3.38	23.8	0.97			97			47			25	24	
13.5	300		149	35	100.0	3.67	3.58	24.0	1.03			107			41			26	27	
14.0	300		155	37	100.4	3.88	3.80	24.5	1.02			99			46			25	26	
14.5	330		158	39	111.6	4.11	3.96	25.1	1.04			101			46			26	27	
15.0	330		162	48	142.4	4.81	4.31	26.6	1.12			102			46			29	32	
15.5	360		166	48	144.8	4.97	4.46	26.9	1.11			108			41			28	32	
16.0	360		168	53	162.6	5.38	4.64	27.6	1.16			115			38			29	34	
16.5	390		171	50	149.1	5.31	4.71	27.5	1.13			106			44			27	31	
17.0	390		175	63	186.0	6.01	4.95	28.3	1.21			116			38			30	36	
17.5	Recovery		161	46	133.7	4.63	3.64	22.6	1.27			111			44			28	36	
18.0	Recovery		134	38	99.1	3.29	2.05	15.3	1.60			119			40			29	47	

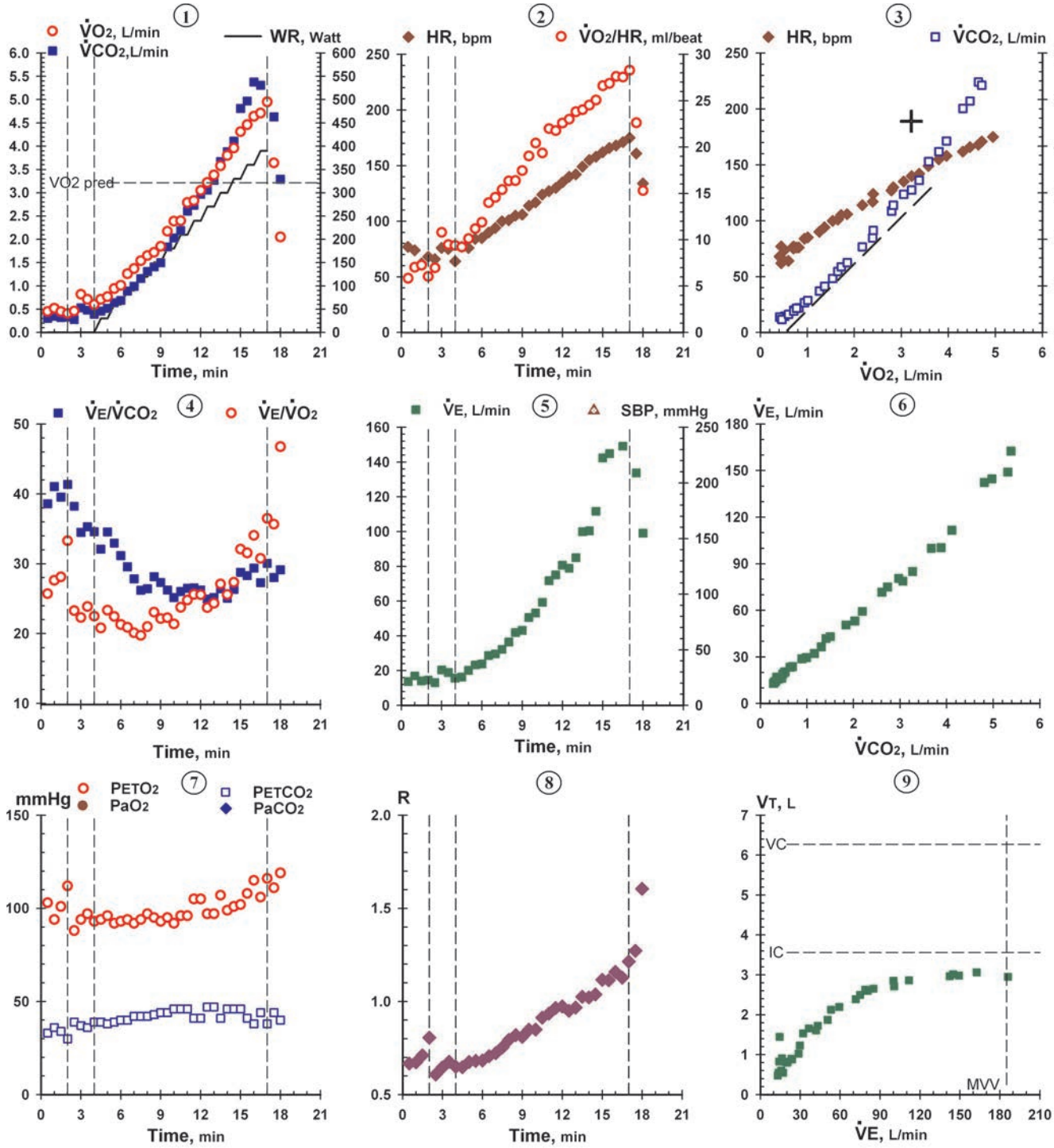

FIGURE 10.2.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 30 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 3 Normal Woman: Air and Oxygen Breathing Studies

CLINICAL FINDINGS

A 45-year-old woman was referred for evaluation of dyspnea. She had recently begun to increase her physical activities and felt that she was more short of breath than she should be. She had no significant medical problems and physical and laboratory examinations revealed no abnormalities.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. She pedaled at 60 rpm without added load for 2 minutes. The work rate was then increased 10 W per minute to her symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter (Fig. 10.3.1). A second incremental exercise test was performed with O_2 breathing 1.5 hours after recovery from the first test, with work rate increments of 20 W per minute (Fig. 10.3.2). She stopped exercise in each case complaining of general fatigue and shortness of breath. Resting and exercise ECGs were normal.

INTERPRETATION

Comments

Resting respiratory function (Table 10.3.1) and ECG are normal.

Table 10.3.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		45
Sex		Female
Height (cm)		165
Weight (kg)	64	61
Hematocrit (%)		40
VC (L)	3.30	3.21
IC (L)	2.20	1.99
FEV_1 (L)	2.68	2.71
FEV_1/VC (%)	81	84
MVV (L/min)	112	117
DLCO (mL/mm Hg/min)	24.1	21.1

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and anaerobic threshold are normal (Table 10.3.2). See Flowchart 2 (Fig. 8.2) for further analysis. There are no ECG abnormalities, and arterial blood gas values and VD/VT are normal throughout exercise (Table 10.3.3). The patient is not obese (Table 10.3.1). Thus, this patient has normal exercise capacity for her age and there is no physiologic evidence of cardiovascular or pulmonary impairment.

Table 10.3.2

Selected Exercise Data

Measurement	Predicted	Room Air	O_2
Peak work rate (W)		130	160
Peak $\dot{V}O_2$ (L/min)	1.60	1.71	
Maximum heart rate (beats/min)	175	160	155
Maximum O_2 pulse (mL/beat)	9.1	10.7	
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	11.9	
AT (L/min)	>0.78	0.9	
Blood pressure (mm Hg [rest, max])		138/81, 194/81	106/75, 181/88
Maximum $\dot{V}E$ (L/min)		70	54
Exercise breathing reserve (L/min)	>15	47	63
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.8	23.3	21.3
PaO_2 (mm Hg [rest, max ex])		105, 108	643, 552
$P(A-a)O_2$ (mm Hg [rest, max ex])		5, 16	33, 117
$PaCO_2$ (mm Hg [rest, max ex])		38, 33	37, 44
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		−1, −6	4, −3
VD/VT (rest, heavy ex)		0.21, 0.11	0.34, 0.18
HCO_3^- (mEq/L [rest, 2-min recov])		25, 13	25, NA

NA, not available.

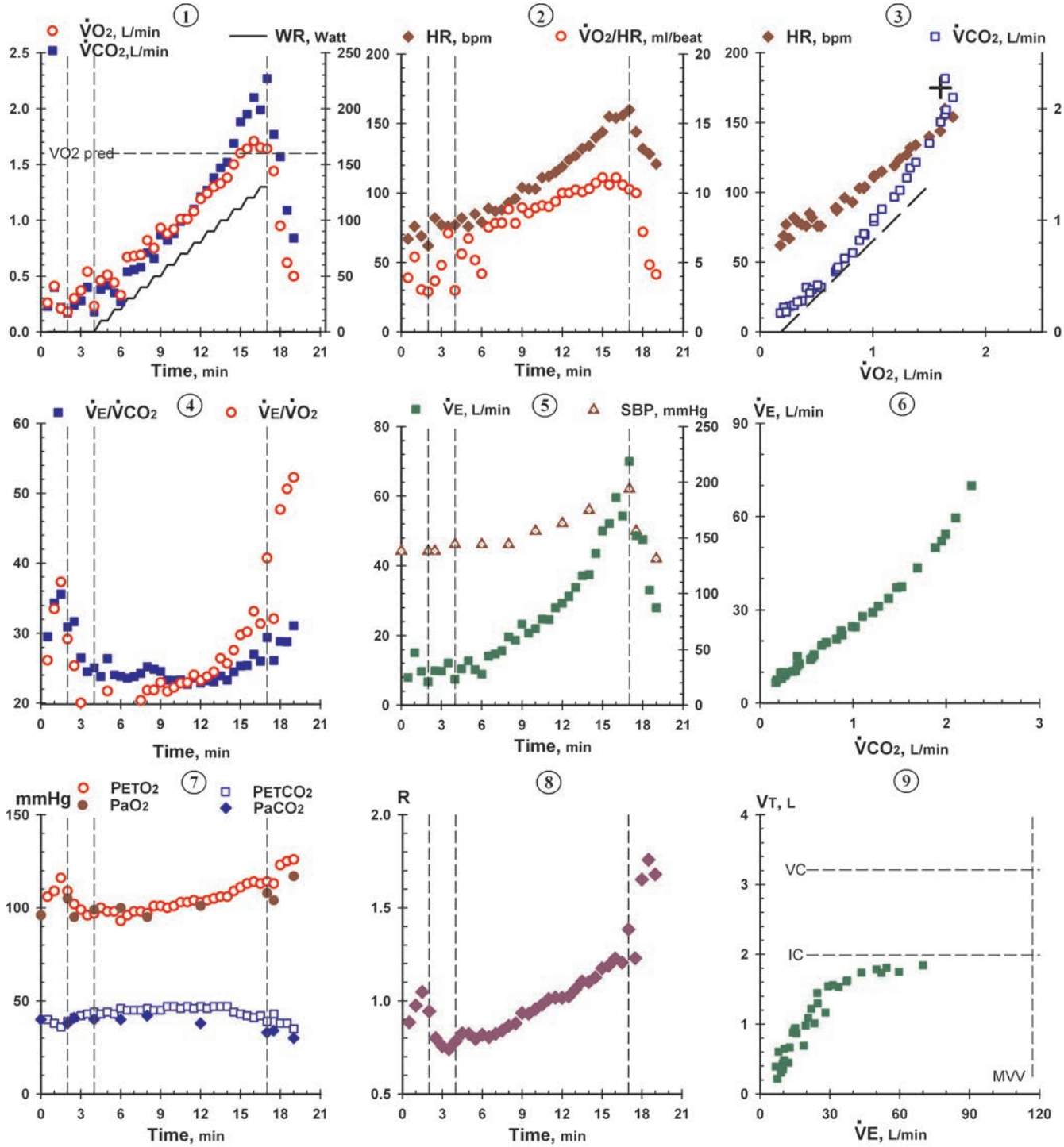

FIGURE 10.3.1. Air breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

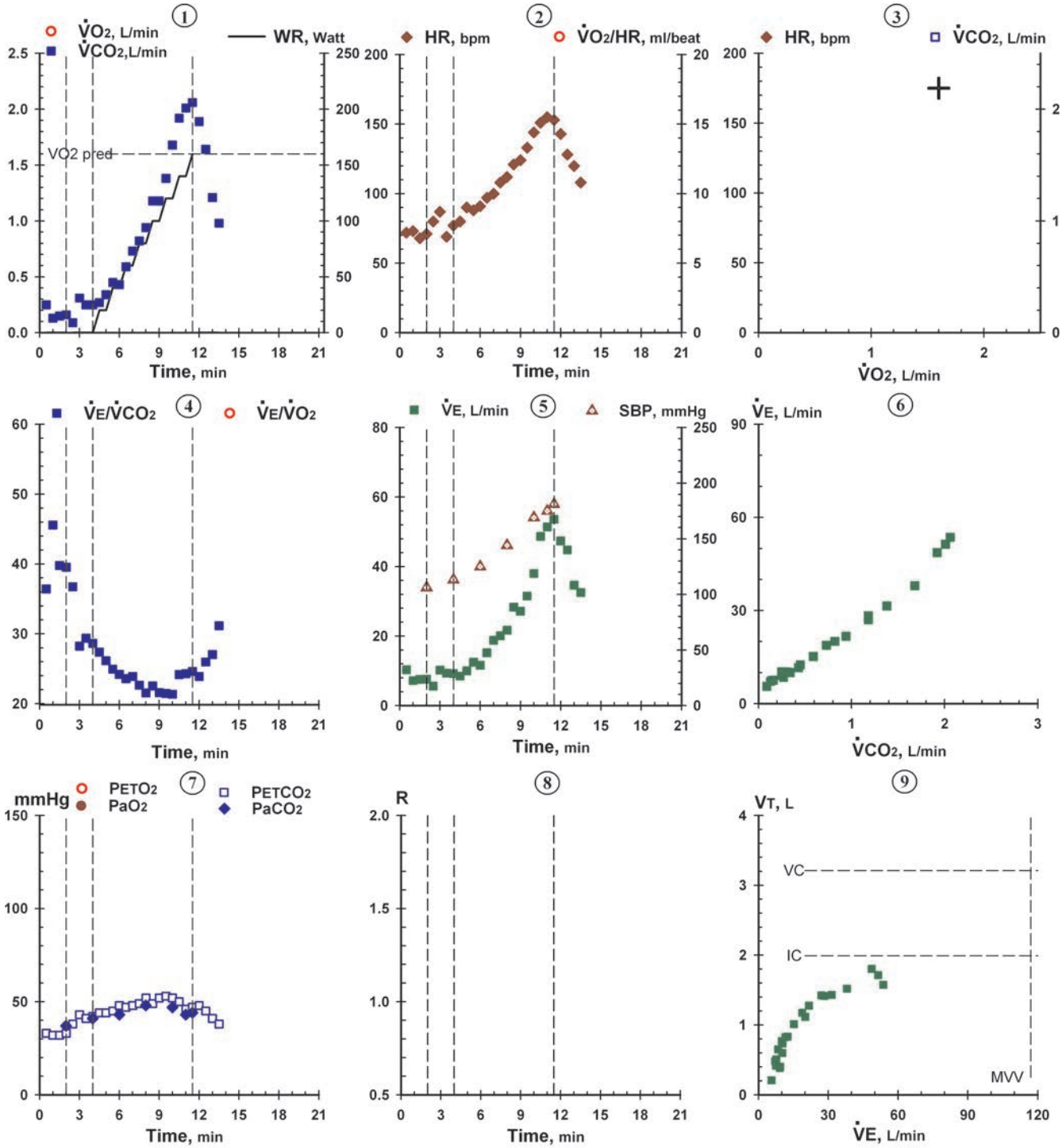

FIGURE 10.3.2. 100% oxygen breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. Oxygen uptake data are not shown because of technical limitations of calculation with very high inspired oxygen levels.

Table 10.3.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	138/81								7.42	25		96			40				
1.0	Rest		67	13	7.9	0.23	0.26	3.9	0.88			106			40			30	26	
1.5	Rest		76	16	15.1	0.40	0.41	5.4	0.98			109			38			34	34	
2.0	Rest		69	22	9.7	0.22	0.21	3.0	1.05			116			36			36	37	
2.5	Rest	138/75	62	17	6.7	0.17	0.18	2.9	0.94	7.43	25	109	105	5	39	38	–1	31	29	0.21
3.0	Unloaded	138/81	82	27	9.9	0.24	0.30	3.7	0.80	7.41	26	102	95	6	41	41	0	32	25	0.26
3.5	Unloaded		77	28	9.8	0.28	0.37	4.8	0.76			99			42			27	20	
4.0	Unloaded		76	27	12.1	0.40	0.54	7.1	0.74			96			43			25	18	
4.5	Unloaded	144/75	77	34	7.4	0.18	0.23	3.0	0.78	7.41	25	97	99	2	44	40	–4	25	20	0.08
5.0	10		82	16	10.4	0.38	0.46	5.6	0.83			100			43			24	20	
5.5	10		76	19	12.7	0.42	0.51	6.7	0.82			98			44			26	22	
6.0	20		85	21	10.2	0.35	0.44	5.2	0.80			98			43			24	19	
6.5	20	144/75	79	29	8.9	0.27	0.33	4.2	0.82	7.41	25	93	100	3	46	40	–6	24	20	0.07
7.0	30		89	16	14.1	0.54	0.67	7.5	0.81			96			45			24	19	
7.5	30		87	16	14.7	0.56	0.68	7.8	0.82			98			45			24	20	
8.0	40		88	18	15.6	0.58	0.69	7.8	0.84			98			45			24	20	
8.5	40	144/75	93	20	19.6	0.71	0.82	8.8	0.87	7.39	25	97	95	8	46	42	–4	25	22	0.17
9.0	50		96	27	18.7	0.66	0.75	7.8	0.88			101			45			25	22	
9.5	50		104	23	23.3	0.87	0.93	8.9	0.94			101			45			25	23	
10.0	60		103	19	20.7	0.82	0.88	8.5	0.93			100			47			23	22	
10.5	60	156/75	103	18	22.0	0.88	0.92	8.9	0.96			101			47			23	22	
11.0	70		111	19	24.7	0.99	1.01	9.0	0.99			103			46			23	23	
11.5	70		112	17	24.6	1.02	1.01	9.0	1.01			103			47			23	23	
12.0	80		115	24	28.0	1.10	1.08	9.4	1.02			104			46			24	24	
12.5	80	163/75	119	19	29.3	1.21	1.19	10.0	1.02	7.37	22	103	101	11	47	38	–9	23	23	0.01
13.0	90		124	20	31.2	1.27	1.24	10.0	1.02			104			46			23	24	
13.5	90		127	22	33.7	1.38	1.30	10.2	1.06			105			47			23	24	
14.0	100		132	23	37.1	1.47	1.33	10.1	1.11			106			47			24	26	
14.5	100	175/81	134	23	37.4	1.52	1.38	10.3	1.10			106			47			23	26	
15.0	110		140	25	43.5	1.69	1.50	10.7	1.13			109			44			24	28	
15.5	110		144	28	50.0	1.88	1.60	11.1	1.18			111			43			25	30	
16.0	120		155	30	52.1	1.95	1.64	10.6	1.19			113			42			25	30	
16.5	120		154	34	59.6	2.10	1.71	11.1	1.23			114			41			27	33	
17.0	130		156	30	54.3	1.99	1.65	10.6	1.21			113			42			26	31	
17.5	130	194/81	160	38	70.0	2.27	1.64	10.3	1.38	7.31	16	114	108	16	39	33	–6	29	41	0.11
18.0	Recovery	156/69	144	28	48.6	1.77	1.44	10.0	1.23	7.28	16	113	104	17	43	34	–9	26	32	0.03
18.5	Recovery		132	26	47.5	1.57	0.95	7.2	1.65			123			38			29	48	
19.0	Recovery		128	19	33.0	1.09	0.62	4.8	1.76			125			38			29	51	
19.5	Recovery	131/63	121	22	28.0	0.84	0.50	4.1	1.68	7.26	13	126	117	13	35	30	–5	31	52	0.07

Pa_{O_2} is also normal during 100% O_2 breathing (Table 10.3.4). Although the $P(A-a)_{O_2}$ is higher during oxygen breathing than during air breathing, the Pa_{O_2} values in excess of 550 mm Hg throughout exercise on oxygen breathing rules out a significant right-to-left shunt. Of note is that the patient was able to exercise to a higher work rate with a slightly lower heart rate during O_2 breathing compared to air breathing. Moreover, respiratory compensation for the metabolic acidosis (decrease in Pa_{CO_2}) was less evident during the O_2 breathing study.

Conclusion

Our final assessment is that this patient was normal, although of below-average fitness, and that her symptoms arose from her previously sedentary activity pattern.

Table 10.3.4

Oxygen Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	*a*	(*A* − *a*)	*ET*	*a*	(*a* − *ET*)			
0.5	Rest		72	14	10.3	0.25									33			36		
1.0	Rest		73	15	7.2	0.13									32			46		
1.5	Rest		68	18	7.5	0.15									32			40		
2.0	Rest	106/75	71	15	7.6	0.16				7.44	25		643	33	33	37	4	40		0.34
2.5	Unloaded		80	27	5.6	0.09									38			37		
3.0	Unloaded		87	17	10.2	0.31									43			28		
3.5	Unloaded		69	23	9.3	0.25									41			29		
4.0	Unloaded	113/69	77	24	9.2	0.25				7.39	24		605	67	42	41	–1	29		0.21
4.5	20		80	13	8.5	0.27									44			27		
5.0	20		90	13	10.0	0.34									44			26		
5.5	40		88	15	12.5	0.45									45			25		
6.0	40	125/69	91	14	11.6	0.43				7.39	26		595	75	48	43	–5	24		0.15
6.5	60		97	15	15.2	0.59									47			24		
7.0	60		100	16	18.8	0.73									48			24		
7.5	80		108	18	20.1	0.82									49			23		
8.0	80	144/75	112	17	21.7	0.94				7.34	25		601	64	52	48	–4	22		0.15
8.5	100		121	20	28.3	1.18									49			23		
9.0	100		124	19	27.1	1.18									52			22		
9.5	120		133	22	31.5	1.38									53			21		
10.0	120	169/81	144	25	38.0	1.68				7.29	22		587	79	52	47	–5	21		0.13
10.5	140		151	27	48.7	1.92									50			24		
11.0	140	175/81	155	30	51.4	2.01				7.30	21		564	106	46	43	–3	24		0.17
11.5	160	181/88	153	34	53.6	2.06				7.28	20		552	117	47	44	–3	25		0.19
12.0	Recovery		143	26	47.4	1.89									48			24		
12.5	Recovery		128	26	44.8	1.64									45			26		
13.0	Recovery		120	22	34.6	1.21									41			27		
13.5	Recovery		108	23	32.5	0.98									38			31		

Case 4 Normal Man

CLINICAL FINDINGS

A 37-year-old shipyard machinist was evaluated because of complaints of dyspnea. He stated that he has been unable to play a full game of baseball for the last 6 years. He gets out of breath and has to stop after climbing three to four flights of stairs when working on shipboard. He never smoked. He denied cough, chest pain, edema, or other symptoms. Physical, roentgenographic, and laboratory examinations were normal.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 25 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. He stopped exercise because of general fatigue. Resting and exercise ECGs were normal.

INTERPRETATION

Comments

The results of this patient's resting respiratory function studies are normal (Table 10.4.1). The resting ECG is normal.

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ and the anaerobic threshold are within normal limits (Tables 10.4.2 and 10.4.3). See Flowchart 2 (Fig. 8.2) for further details. ECG, and, as shown in Figure 10.4.1, O_2 pulse at peak $\dot{V}O_2$, and arterial blood gases are normal (branch point 2.1 of Fig. 8.2). The patient is not obese (branch point 2.2 of Fig. 8.2).

Conclusion

This is a normal 37-year-old man. Symptoms probably relate to lack of fitness.

Table 10.4.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		37
Sex		Male
Height (cm)		157
Weight (kg)	63	67
Hematocrit (%)		45
VC (L)	3.30	4.38
IC (L)	2.20	2.80
TLC (L)	4.52	5.30
FEV_1 (L)	2.66	3.52
FEV_1/VC (%)	81	80
MVV (L/min)	127	124
DLCO (mL/mm Hg/min)	22.4	29.8

Table 10.4.2

Selected Exercise Data

Measurement	Predicted	Measured
Maximum $\dot{V}O_2$ (L/min)	2.36	2.23
Maximum heart rate (beats/min)	183	188
Maximum O_2 pulse (mL/beat)	12.9	11.9
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	10.4
AT (L/min)	>0.99	1.1
Blood pressure (mm Hg [rest, max])		125/75, 188/94
Maximum $\dot{V}E$ (L/min)		90
Exercise breathing reserve (L/min)	>15	34
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.2	25.8
PaO_2 (mm Hg [rest, max ex])		84, 114
$P(A-a)O_2$ (mm Hg [rest, max ex])		7, 2
$PaCO_2$ (mm Hg [rest, max ex])		40, 38
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		0, −4
VD/VT (rest, heavy ex)		0.31, 0.16
HCO_3^- (mEq/L [rest, 2-min recov])		24, 16

Table 10.4.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	125/75	7.41	24						7.41	24		103			39				
0.5	Rest		77	11	6.4	0.16	0.29	2.5	0.84			108			37			34	29	
1.0	Rest		78	14	7.5	0.18	0.23	2.9	0.78			107			36			35	27	
1.5	Rest		72	15	9.0	0.22	0.29	4.0	0.76			106			36			35	27	
2.0	Rest		78	13	7.1	0.16	0.20	2.6	0.80			108			35			37	30	
2.5	Rest		78	11	6.0	0.16	0.23	2.9	0.70			98			39			32	22	
3.0	Rest	125/81	82	13	6.9	0.17	0.27	3.3	0.63	7.39	24	94	84	7	40	40	0	34	21	0.31
3.5	Unloaded		83	21	9.0	0.26	0.40	4.8	0.65			80			47			28	18	
4.0	Unloaded		94	28	16.7	0.53	0.46	4.9	1.15			93			42			27	31	
4.5	Unloaded		93	38	12.1	0.32	0.44	4.7	0.73			92			44			28	20	
5.0	Unloaded		95	31	14.4	0.41	0.57	6.0	0.72			95			44			29	21	
5.5	Unloaded		93	23	11.5	0.34	0.45	4.8	0.76			96			44			28	21	
6.0	Unloaded	144/81	96	28	15.6	0.49	0.61	6.4	0.80	7.37	24	98	91	8	43	43	0	27	22	0.22
6.5	25		98	25	17.5	0.53	0.66	6.7	0.80			97			43			29	23	
7.0	25		102	26	16.6	0.50	0.67	6.6	0.75			96			43			29	21	
7.5	50		109	28	21.6	0.69	0.92	8.4	0.75			97			42			28	21	
8.0	50	150/81	117	25	23.5	0.82	1.08	9.2	0.76	7.38	25	95	95	1	44	43	–1	26	20	0.21
8.5	75		126	26	25.5	0.91	1.12	8.9	0.81			98			44			26	21	
9.0	75		127	27	27.7	1.01	1.19	9.4	0.85			99			45			25	21	
9.5	100		138	29	33.6	1.26	1.39	10.1	0.91			101			45			25	22	
10.0	100	181/94	141	32	38.6	1.47	1.54	10.9	0.95	7.37	24	102	104	2	45	42	–3	24	23	0.15
10.5	125		151	41	49.7	1.74	1.68	11.1	1.04			108			43			27	28	
11.0	125		162	40	53.5	1.92	1.78	11.0	1.08			110			42			26	28	
11.5	150		169	39	60.2	2.17	1.94	11.5	1.12			111			42			26	29	
12.0	150	188/94	176	46	68.8	2.36	2.04	11.6	1.16	7.37	22	112	114	2	42	38	–4	27	32	0.16
12.5	175		182	50	76.0	2.51	2.11	11.6	1.19			114			41			29	34	
13.0	175		188	51	89.7	2.84	2.23	11.9	1.27			118			38			30	38	
13.5	Recovery		178	31	59.6	2.17	1.83	10.3	1.19			111			43			26	31	
14.0	Recovery		161	29	47.5	1.66	1.19	7.4	1.39			116			41			27	38	
14.5	Recovery		144	27	42.0	1.37	0.84	5.8	1.63			123			37			29	47	
15.0	Recovery	181/100	136	28	37.5	1.08	0.62	4.6	1.74	7.30	16	127	126	2	35	33	–2	33	57	0.18
15.5	Recovery		135	24	23.9	0.68	0.44	3.3	1.55			124			36			32	50	

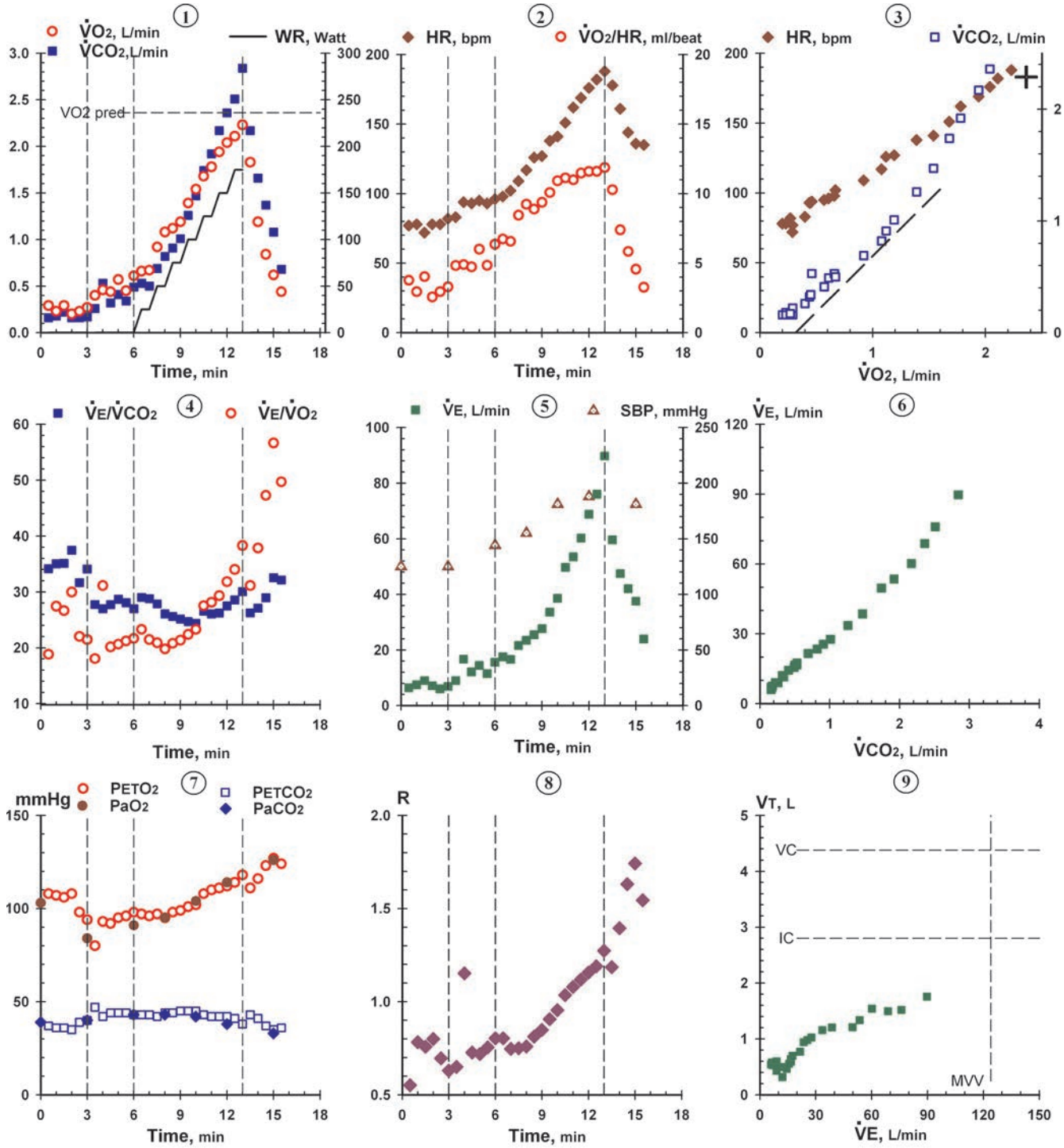

FIGURE 10.4.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 25 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 5 Exceptionally Fit Man with Mild Lung Disease

CLINICAL FINDINGS

A 59-year-old shipyard worker had no complaints or history of heart or lung disease. He had sustained a gunshot wound to the right chest at age 24 that was not surgically treated. He had been exposed to asbestos 20 years previously and had smoked one pack of cigarettes daily for 12 years until 20 years ago. He bicycled approximately 50 miles a week. Physical, roentgenographic, and ECG examinations were normal except for evidence of focal, old granulomatous disease and an old rib fracture.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 20 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. He stopped exercise because of general exhaustion. Exercise ECGs were normal.

INTERPRETATION

Comments

The results of this patient's respiratory function studies are within normal limits (Table 10.5.1). The resting ECG is normal. When starting to breathe on the mouthpiece at rest, the patient hyperventilated to a pH of 7.52, $P_{A}CO_2$ of 27 mm Hg, and $P_{A}O_2$ of 120. The respiratory alkalosis was acute, developing in anticipation of exercise or in response to the breathing apparatus. It resolved after exercise started. The unusually large increase in $P_{A}O_2$ when starting to breathe on the mouthpiece at rest was probably due to (1) reversal of hypoxemia off the mouthpiece due to microatelectasis associated with obesity (a common problem in overweight subjects); and (2) the large increase in $P_{A}O_2$, which accompanies acute hyperventilation, and a high respiratory exchange ratio (R).

Table 10.5.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		59
Sex		Male
Height (cm)		175
Weight (kg)	78	93
Hematocrit (%)		46
VC (L)	4.21	4.34
IC (L)	2.79	3.57
TLC (L)	6.36	5.86
FEV_1 (L)	3.58	3.57
FEV_1/VC (%)	80	82
MVV (L/min)	137	152
D_{LCO} (mL/mm Hg/min)	28.2	29.5

Analysis

Referring to Flowchart 1 (Fig. 8.1), this patient's peak $\dot{V}O_2$ and anaerobic threshold are above predicted (Table 10.5.2). Because he cycled regularly, he performed exceedingly well with this modality of testing. Referring

Table 10.5.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.32	3.40
Maximum heart rate (beats/min)	161	195
Maximum O_2 pulse (mL/beat)	14.4	17.4
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	12.7
AT (L/min)	>1.02	1.4
Blood pressure (mm Hg [rest, max])		125/75, 200/88
Maximum $\dot{V}_E$ (L/min)		174
Exercise breathing reserve (L/min)	>15	−22
$\dot{V}_E/\dot{V}CO_2$ @ *AT* or lowest	27.9	25.7
$P_{A}O_2$ (mm Hg [rest, max ex])		120, 71
$P(A-a)O_2$ (mm Hg [rest, max ex])		5, 49
$P_{A}CO_2$ (mm Hg [rest, max ex])		27, 34
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		−4, −13
V_D/V_T (rest, heavy ex)		0.17, 0.02
HCO_3^- (mEq/L [rest, 2-min recov])		25, 10

to Flowchart 2 (Fig. 8.2), the ECG and O_2 pulse (high because of fitness) at maximal exercise are normal. Of note, although the O_2 pulse reaches a constant level over the last several minutes of exercise (Fig. 10.5.1, panel 2), this is not considered abnormal because the value of the O_2 pulse is not reduced. Blood gases (Table 10.5.3) are not entirely normal (branch point 2.1 of Fig. 8.2). V_D/V_T and $P(a-ET)CO_2$ are normal, but $P(A-a)O_2$ at maximum exercise is increased (Table 10.5.3 and Fig. 10.5.1) and suggests the presence of mild lung disease (branch point 2.3 of Fig. 8.2).

Conclusion

This exceptionally fit man of 59 years has normal exercise function, and a subtle finding of mild lung disease.

Table 10.5.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	125/75								7.45	25		75			36				
0.5	Rest		77	11	20.9	0.48	0.36	4.7	1.33			123			30			42	55	
1.0	Rest		77	17	17.3	0.36	0.28	3.6	1.29			124			29			44	57	
1.5	Rest		79	11	16.2	0.39	0.34	4.3	1.15			122			29			39	45	
2.0	Rest	119/75	84	8	14.6	0.36	0.33	3.9	1.09	7.52	22	118	120	5	31	27	−4	39	42	0.17
2.5	Unloaded		96	7	16.4	0.54	0.67	7.0	0.81			97			39			29	24	
3.0	Unloaded		84	12	21.9	0.65	0.74	8.8	0.88			106			36			32	28	
3.5	Unloaded		81	13	23.9	0.68	0.72	8.9	0.94			110			35			34	32	
4.0	Unloaded		81	17	26.2	0.68	0.70	8.6	0.97			111			34			36	35	
4.5	Unloaded		82	10	23.0	0.66	0.71	8.7	0.93			108			35			34	31	
5.0	Unloaded	156/81	82	16	23.3	0.65	0.69	8.4	0.94	7.47	22	110	103	14	35	31	−4	34	32	0.17
5.5	20		79	15	24.7	0.73	0.82	10.4	0.89			107			35			32	29	
6.0	20		84	18	23.3	0.70	0.78	9.3	0.90			99			39			31	28	
6.5	40		82	8	18.9	0.66	0.88	10.7	0.75			91			41			28	21	
7.0	40	163/81	89	8	24.0	0.87	1.11	12.5	0.78	7.43	24	92	77	28	42	37	−5	27	21	0.13
7.5	60		91	13	23.5	0.89	1.15	12.6	0.77			89			44			25	19	
8.0	60		99	16	24.2	0.90	1.18	11.9	0.76			84			47			25	19	
8.5	80		98	21	35.2	1.28	1.53	15.6	0.84			78			50			26	22	
9.0	80	175/81	107	14	36.1	1.38	1.54	14.4	0.90	7.41	24	95	85	24	45	38	−7	25	23	0.10
9.5	100		107	15	41.1	1.55	1.63	15.2	0.95			96			47			26	24	
10.0	100		113	16	43.4	1.72	1.82	16.1	0.95			97			47			24	23	
10.5	120		117	22	52.0	1.93	1.95	16.7	0.99			99			45			26	26	
11.0	120		123	20	56.5	2.08	2.07	16.8	1.00	7.37	21	99	86	27	46	37	−9	26	26	0.11
11.5	140		119	20	60.0	2.20	2.17	18.2	1.01			100			46			27	27	
12.0	140		128	21	61.2	2.33	2.26	17.7	1.03			101			46			26	26	
12.5	160		131	25	72.5	2.61	2.44	18.6	1.07			105			44			27	29	
13.0	160	200/88	147	21	69.8	2.65	2.50	17.0	1.06	7.35	18	102	75	43	46	34	−12	26	27	0.01
13.5	180		148	27	82.1	3.03	2.74	18.5	1.11			106			44			26	29	
14.0	180		161	26	82.2	3.11	2.79	17.3	1.11			104			46			26	29	
14.5	200		166	26	85.0	3.24	2.85	17.2	1.14			104			47			26	29	
15.0	200		167	30	90.6	3.40	2.90	17.4	1.17	7.29	16	106	71	49	47	34	−13	26	30	0.02
15.5	220		176	31	105.5	3.74	3.06	17.4	1.22			109			44			28	34	
16.0	220		189	34	117.3	4.01	3.13	16.6	1.28			112			42			29	37	
16.5	240		195	55	174.5	4.75	3.40	17.4	1.40			122			34			36	50	
17.0	Recovery	200/88	180	35	121.1	3.52	2.68	14.9	1.31	7.26	13	118	83	43	36	29	−7	34	44	0.11
17.5	Recovery		171	33	113.3	3.15	1.99	11.6	1.58			118			38			35	56	
18.0	Recovery		159	26	89.2	2.42	1.35	8.5	1.79			125			36			36	64	
18.5	Recovery	163/75	147	28	83.7	2.01	1.09	7.4	1.84	7.20	10	128	113	20	32	26	−6	40	75	0.17
19.0	Recovery		145	27	67.1	1.50	0.90	6.2	1.67			128			31			43	72	

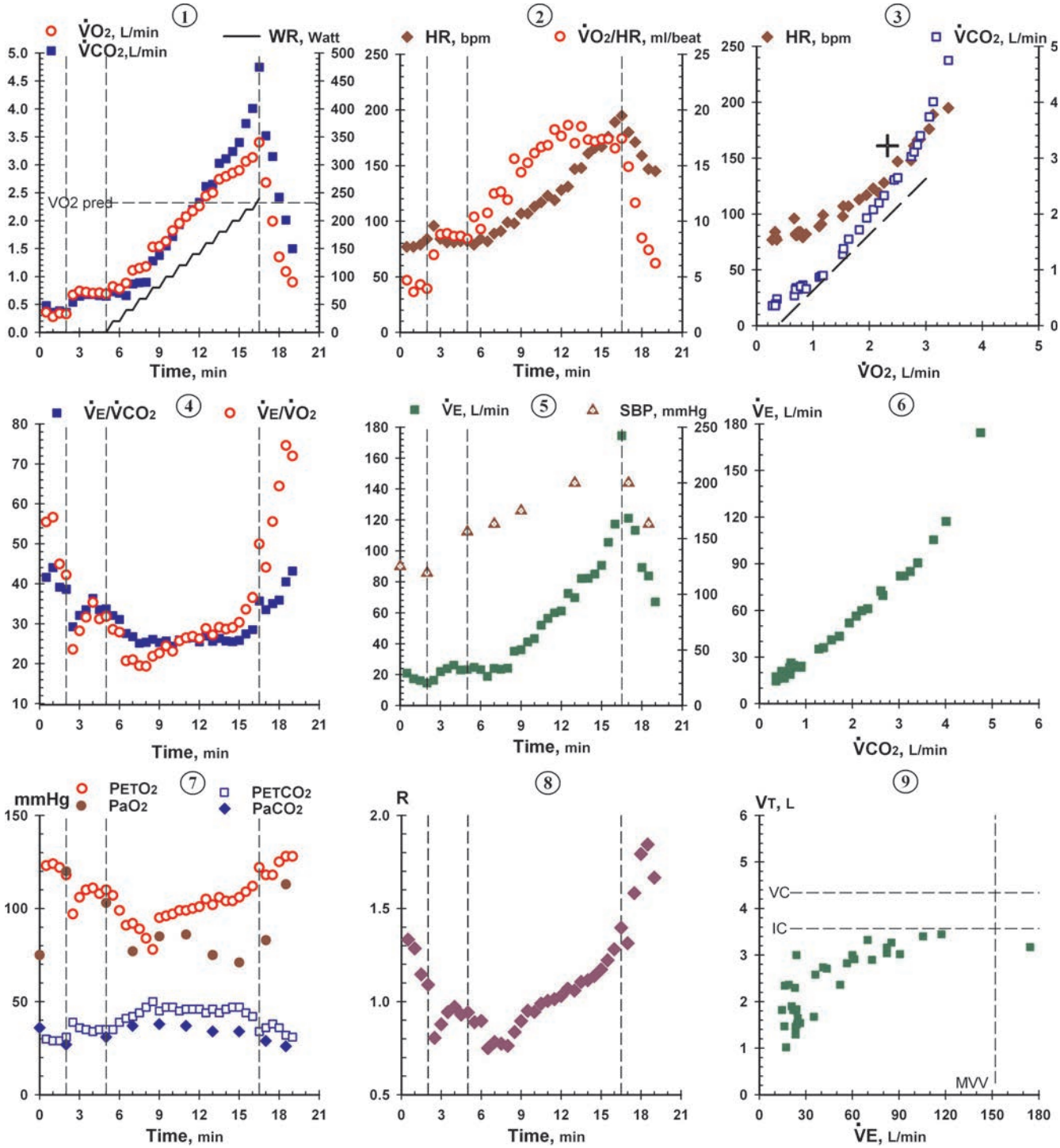

FIGURE 10.5.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 6 Normal Subject: Cycle and Treadmill Studies

CLINICAL FINDINGS

A 37-year-old hospital employee was asymptomatic and volunteered for an exercise study. He did not exercise regularly or smoke. Physical examination, chest roentgenograms, and resting ECG were normal.

EXERCISE FINDINGS

On two separate days, 1 month apart, the subject exercised to maximum tolerance using incremental exercise protocols, first on the cycle and second on the treadmill. He stopped on both occasions because of calf fatigue. There were no arrhythmias or abnormalities in the ECG.

Table 10.6.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		37
Sex		Male
Height (cm)		161
Weight (kg)	66	53
Hematocrit (%)		45
VC (L)	3.56	3.21
IC (L)	2.37	2.51
TLC (L)	4.90	5.01
FEV_1 (L)	2.87	2.64
FEV_1/VC (%)	81	82
MVV (L/min)	132	107
D_{LCO} (mL/mm Hg/min)	23.1	22.3

INTERPRETATION

Comments

The results of this subject's resting respiratory function studies were normal (Table 10.6.1). The resting ECG was normal. This study is presented to contrast the results when the same subject performed on the cycle and on the treadmill. The summary physiological responses to the cycle and treadmill exercise studies are provided in Table 10.6.2. The detailed physiological responses for both forms of ergometry are given in Tables 10.6.3 and 10.6.4 and Figures 10.6.1 and 10.6.2.

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and the anaerobic threshold were normal for both cycle and treadmill exercise (Table 10.6.2). Referring to Flowchart 2 (Fig. 8.2), the ECG and O_2 pulse were normal at maximum work rate (branch point 2.1 of Fig. 8.2). The subject was not obese (branch point 2.2 of Fig. 8.2). The peak $\dot{V}O_2$ was about 10% higher on the treadmill than on the cycle.

Conclusion

This subject has exercise capacity in the lower range of normal. The finding of slightly higher peak $\dot{V}O_2$ on treadmill testing compared to cycle testing is typical for subjects who do not cycle regularly.

Table 10.6.2

Selected Exercise Data

	Predicted		Measured	
Measurement	Cycle	Treadmill	Cycle	Treadmill
Peak $\dot{V}O_2$ (L/min)	2.21	2.45	1.87	2.07
Maximum heart rate (beats/min)	183	183	173	183
Maximum O_2 pulse (mL/beat)	12.1	13.4	10.8	11.3
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3		8.4	
AT (L/min)	>0.93	>1.03	1.1	1.15
Maximum $\dot{V}E$ (L/min)			76	85
Exercise breathing reserve (L/min)	>15	>15	31	22
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.1	26.1	21.7	23.8

Table 10.6.3

Cycle Ergometry

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest		79	15	9.5	0.28	0.33	4.2	0.85			99			44			29	25	
1.0	Rest		95	14	11.1	0.36	0.42	4.4	0.86			97			45			28	24	
1.5	Rest		78	13	7.8	0.23	0.26	3.3	0.88			101			44			29	26	
2.0	Rest		74	14	7.3	0.19	0.21	2.8	0.90			102			43			32	29	
2.5	Unloaded		109	18	17.3	0.58	0.55	5.0	1.05			105			44			27	29	
3.0	Unloaded		97	8	11.1	0.44	0.52	5.4	0.85			96			46			24	20	
3.5	Unloaded		103	17	14.3	0.53	0.63	6.1	0.84			92			48			24	20	
4.0	Unloaded		104	16	15.1	0.56	0.65	6.3	0.86			94			47			25	21	
4.5	Unloaded		108	16	17.7	0.67	0.71	6.6	0.94			97			47			24	23	
5.0	Unloaded		97	16	14.8	0.55	0.55	5.7	1.00			103			46			24	24	
5.5	25		107	16	16.4	0.61	0.60	5.6	1.02			104			46			25	25	
6.0	25		108	18	16.2	0.57	0.57	5.3	1.00			103			45			26	26	
6.5	50		113	18	15.8	0.58	0.64	5.7	0.91			96			47			25	22	
7.0	50		110	17	17.1	0.67	0.74	6.7	0.91			94			50			23	21	
7.5	75		122	19	22.0	0.86	0.89	7.3	0.97			99			48			24	23	
8.0	75		129	17	19.8	0.85	0.90	7.0	0.94			93			52			22	20	
8.5	100		132	21	26.4	1.07	1.04	7.9	1.03			99			50			23	24	
9.0	100		133	17	22.9	1.07	1.12	8.4	0.96			89			57			20	19	
9.5	125		143	21	31.1	1.40	1.29	9.0	1.09			97			55			21	23	
10.0	125		147	22	35.1	1.64	1.50	10.2	1.09			95			56			20	22	
10.5	150		155	26	41.1	1.82	1.52	9.8	1.20			102			53			22	26	
11.0	150		159	27	44.4	1.94	1.58	9.9	1.23			103			53			22	27	
11.5	175		168	31	53.2	2.24	1.71	10.2	1.31			107			53			23	30	
12.0	175		173	44	75.8	2.79	1.87	10.8	1.49			114			46			26	29	
12.5	Recovery		167	34	60.1	2.31	1.67	10.0	1.38			109			50			25	34	
13.0	Recovery		158	30	49.5	1.88	1.29	8.2	1.46			112			49			25	36	
13.5	Recovery		146	31	48.8	1.68	0.98	6.7	1.71			118			44			27	47	
14.0	Recovery		140	27	40.1	1.30	0.73	5.2	1.78			121			42			29	52	

Table 10.6.4

Treadmill Ergometry

Time (min)	Treadmill Grade (%)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	*a*	$(A-a)$	*ET*	*a*	$(a-ET)$			
0.5	Rest		87	16	8.0	0.20	0.21	2.4	0.95			105			40			33	32	
1.0	Rest		85	19	12.2	0.34	0.37	4.4	0.92			105			40			31	29	
1.5	Rest		81	19	8.6	0.20	0.23	2.8	0.87			106			40			35	30	
2.0	Rest		95	20	13.0	0.34	0.37	3.9	0.92			105			40			33	31	
2.5	0		107	22	14.6	0.47	0.45	4.2	1.04			103			44			27	28	
3.0	0		109	23	19.4	0.62	0.71	6.5	0.87			100			43			28	25	
3.5	3		109	22	19.1	0.63	0.76	7.0	0.83			97			44			27	23	
4.0	3		113	22	22.1	0.77	0.93	8.2	0.83			90			47			26	22	
4.5	6		116	23	21.9	0.77	0.88	7.6	0.88			97			47			26	23	
5.0	6		120	22	25.1	0.94	1.05	8.8	0.90			97			47			25	22	
5.5	9		124	22	27.5	1.06	1.11	9.0	0.95			98			48			24	23	
6.0	9		129	24	30.4	1.17	1.20	9.3	0.98			101			47			24	24	
6.5	12		138	28	35.0	1.31	1.30	9.4	1.01			102			47			25	25	
7.0	12		141	25	35.6	1.43	1.38	9.8	1.04			101			48			23	24	
7.5	15		144	27	38.6	1.53	1.45	10.1	1.06			100			50			24	25	
8.0	15		150	26	39.8	1.59	1.44	9.6	1.10			102			49			24	26	
8.5	18		155	29	45.6	1.82	1.58	10.2	1.15			104			49			24	27	
9.0	18		160	27	47.8	1.98	1.67	10.4	1.19			106			48			23	27	
9.5	21		166	30	53.3	2.14	1.73	10.4	1.24			108			48			24	29	
10.0	21		168	32	59.0	2.33	1.85	11.0	1.26			107			48			24	30	
10.5	24		175	37	67.3	2.54	1.89	10.8	1.34			113			45			25	34	
11.0	24		178	39	71.7	2.69	1.99	11.2	1.35			113			45			25	34	
11.5	27		183	43	84.9	2.97	2.07	11.3	1.43			116			43			27	39	
12.0	Recovery		178	28	47.8	1.75	1.26	7.1	1.39			109			49			26	36	
12.5	Recovery		175	37	68.8	2.60	1.85	10.6	1.41			114			46			25	35	
13.0	Recovery		171	37	68.3	2.40	1.57	9.2	1.53			116			45			27	42	
13.5	Recovery		163	35	58.1	1.84	1.20	7.4	1.53			119			40			30	46	
14.0	Recovery		151	37	49.2	1.41	0.86	5.7	1.64			122			38			33	54	

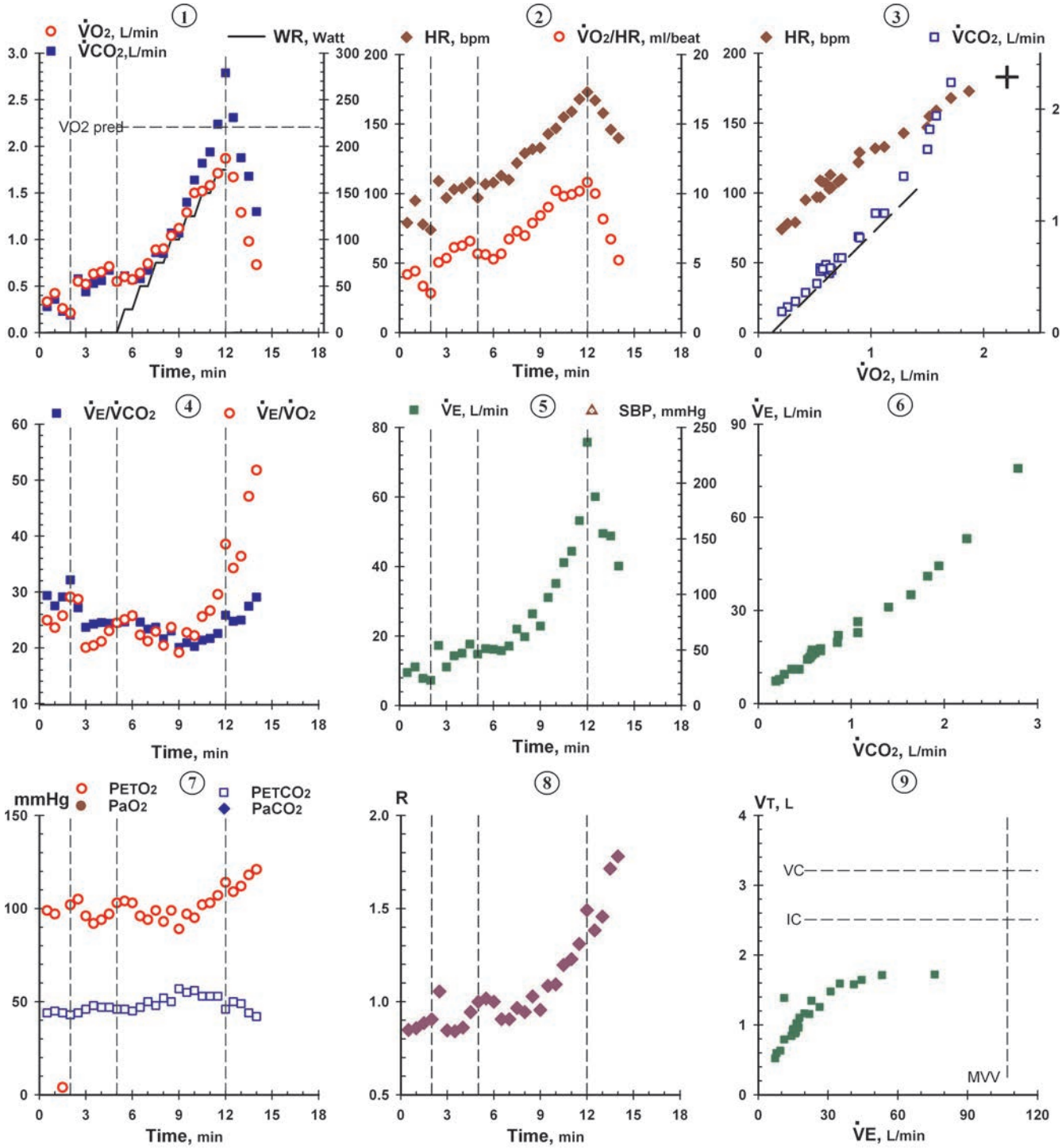

FIGURE 10.6.1. Cycle ergometry. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 25 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

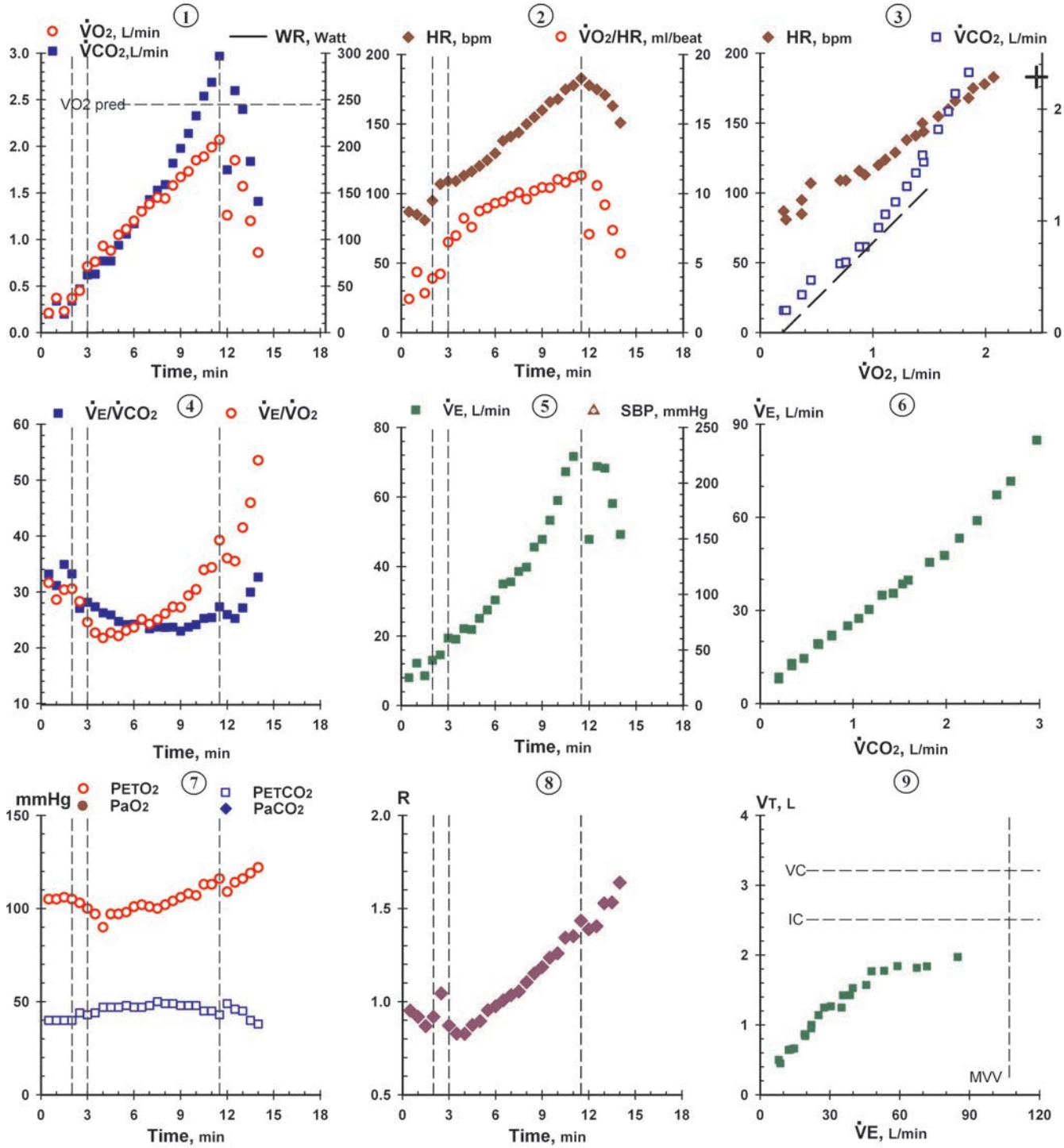

FIGURE 10.6.2. Treadmill ergometry. *Vertical dashed lines* in the panels in the left and middle columns indicate the beginning and end of the incremental exercise period. For 1 minute prior to the first vertical line, the subject walked at zero grade at a speed of 3.0 miles per hour. Thereafter the speed remained constant and grade was increased by 3% each minute. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 7 Normal Subject: Before and After β-Adrenergic Blockade

CLINICAL FINDINGS

A 23-year-old student with stable asthma volunteered for a study evaluating the effect of a β-adrenergic blocker, pindolol, on exercise-induced asthma. He had had hay fever and asthma since childhood but was otherwise in excellent health. He was taking no medications. Physical examination, chest roentgenograms, ECG, and hemogram were normal.

EXERCISE FINDINGS

Two similar cycle exercise studies were performed a week apart. On each occasion, after baseline spirometry, 0.4 mg of pindolol or placebo was given intravenously over a 20-minute period. After repeat spirometry, the subject pedaled without added resistance at 60 rpm for 3 minutes and at 60 W for an additional 3 minutes. Thereafter, the work rate was increased 20 W every minute. On both occasions, the subject stopped because of fatigue. ECG pattern remained normal. Repeat spirometry performed 2, 7, 12, 17, 22, and 27 minutes after exercise did not reveal exercise-induced bronchospasm.

INTERPRETATION

Comments

This study is presented to demonstrate the effect of β-adrenergic blockade on exercise in a healthy subject. Results of respiratory function testing are near normal at the time of study (Table 10.7.1). The usual testing protocol was modified for the purpose of the research study to increase the likelihood of inducing bronchospasm. After unloaded cycling, the work rate was increased immediately to 60 W, followed by 1-minute increments of 20 W. This uneven increase in the work rate increment caused the unusually large increase in $\dot{V}O_2$ after unloaded cycling (panel 1, Figs. 10.7.1 and 10.7.2).

Analysis

Referring to Flowchart 1 (Fig. 8.1), the maximum aerobic capacity and *AT* are within normal limits on both pre- and post-β-adrenergic blockade exercise tests (Table 10.7.2). See Flowchart 2 (Fig. 8.2). The ECG and O_2 pulse at maximum work rate are normal (branch point 2.1 of Fig. 8.2). The large reduction in maximum HR, with slight reduction in peak $\dot{V}O_2$ and increase in maximum O_2 pulse, is typical of the effect of β-adrenergic blockade (Tables 10.7.3 and 10.7.4). The negative chronotropic effect of the β-blockade increases the time for ventricular filling, leading to a larger stroke volume as reflected in a larger O_2 pulse at the same work rate.

Conclusion

These studies are normal, and serve to demonstrate the decrease in heart rate, and lesser decrease in peak $\dot{V}O_2$, following β-adrenergic blockade.

Table 10.7.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		23
Sex		Male
Height (cm)		170
Weight (kg)	68	64
Hematocrit (%)		45
VC (L)	47.9	4.86
IC (L)	3.21	3.40
TLC (L)	6.46	6.72
FEV_1 (L)	4.04	3.58
FEV_1/VC (%)	84	74
MVV (L/min)	175	142
DLCO (mL/mm Hg/min)	33.2	32.5

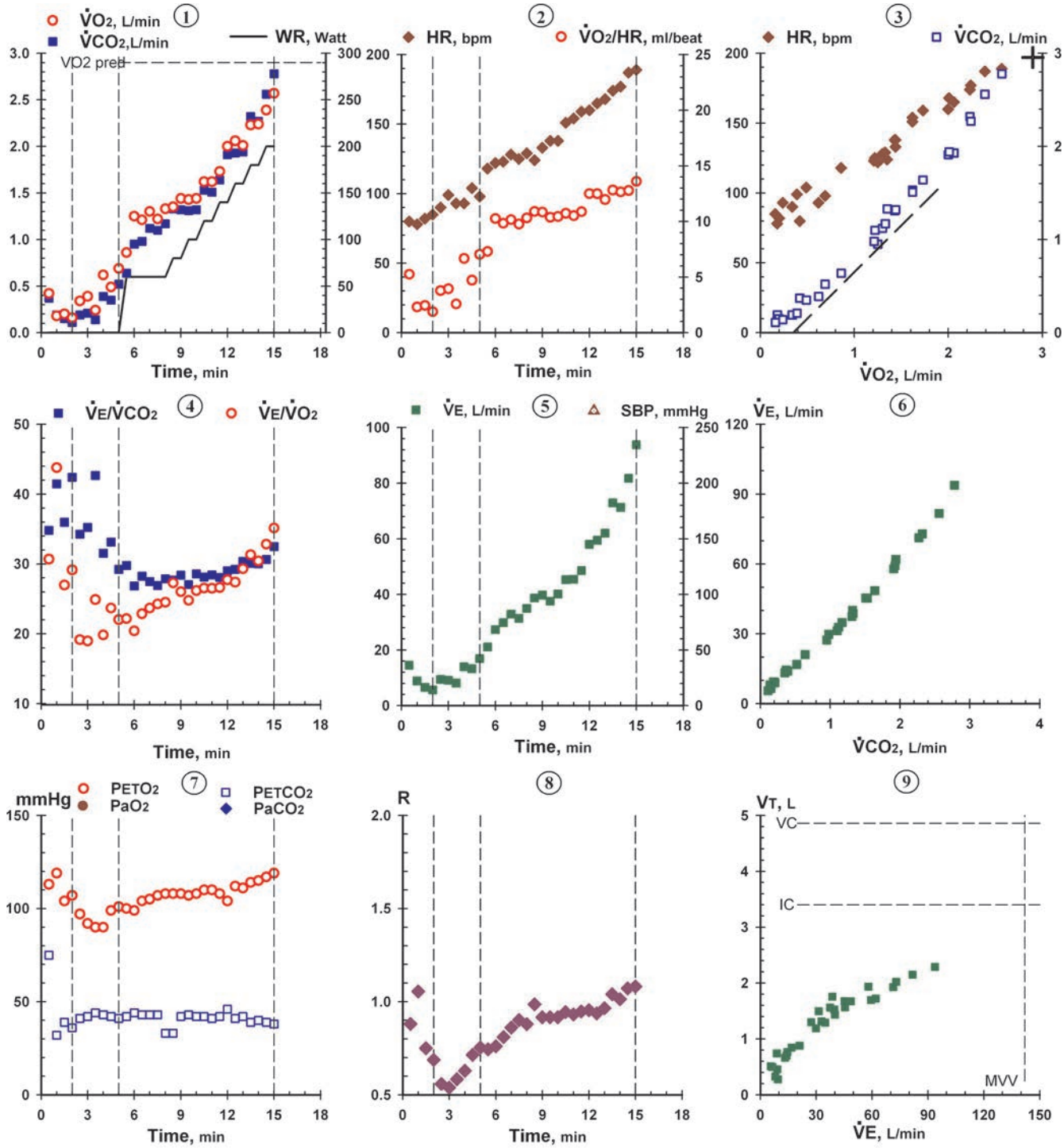

FIGURE 10.7.1. Before β-adrenergic blockade. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate, and start of recovery. Following unloaded cycling, the work rate increased to 60 W for 3 minutes prior to progressively increasing by 20 W per minute. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

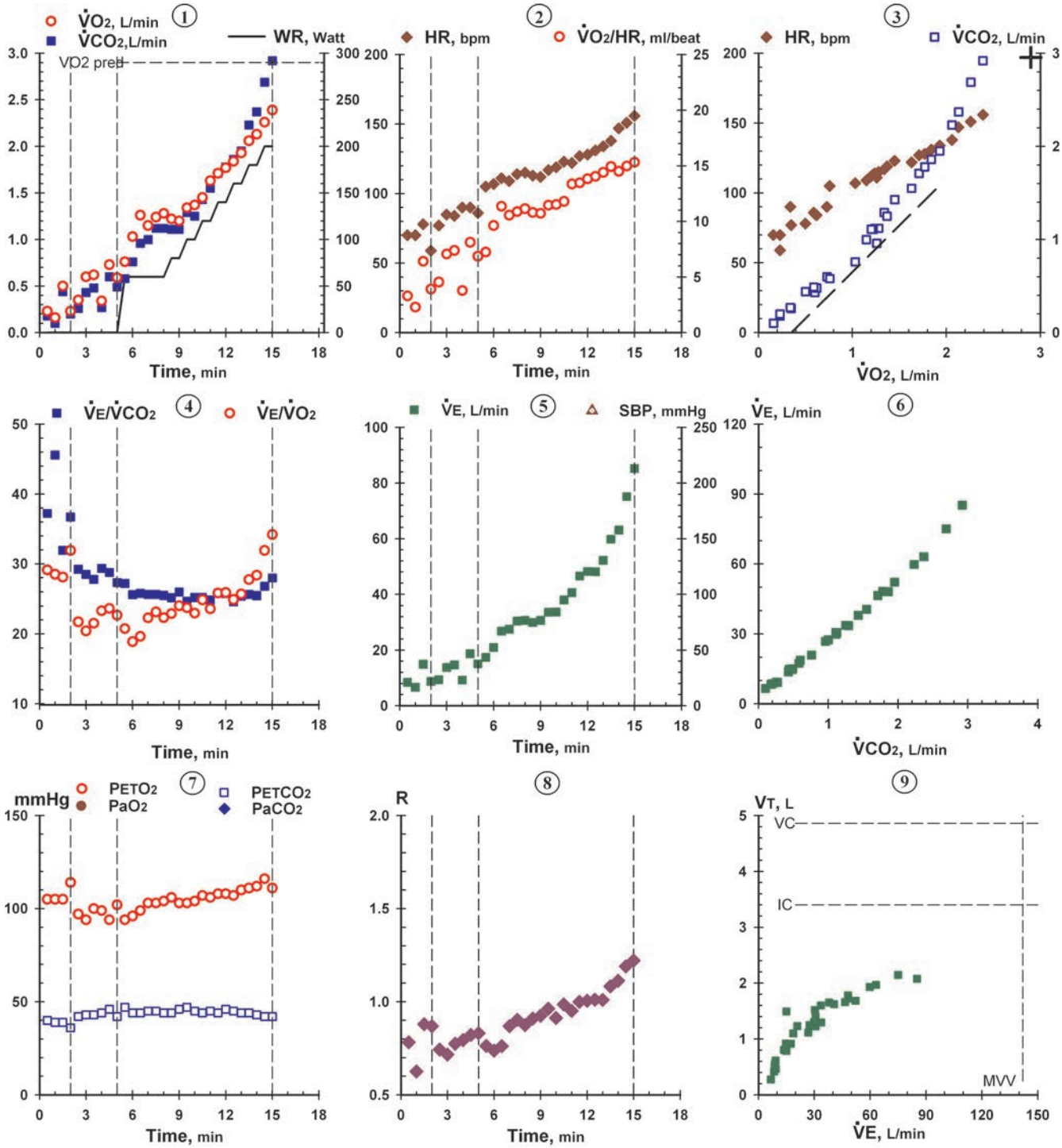

FIGURE 10.7.2. After β-adrenergic blockade. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate, and start of recovery. Following unloaded cycling, the work rate was increased to 60 W for 3 minutes prior to progressively increasing by 20 W per minute. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

TABLE 10.7.2

Selected Exercise Data

Measurement	Predicted	Placebo	Pindolol
Peak $\dot{V}O_2$(L/min)	2.90	2.57	2.39
Maximum heart rate (beats/min)	197	189	156
Maximum O_2 pulse (mL/beat)	14.7	13.6	15.3
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.3	10.5	9.7
AT (L/min)	>1.16	1.5	1.4
Maximum $\dot{V}E$ (L/min)		94	85
Exercise breathing reserve (L/min)	>15	48	57
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	24.3	27.7	25.2

Table 10.7.3

Pre-β-Adrenergic Blockade

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{VD}{VT}$
												ET	*a*	(*A* − *a*)	*ET*	*a*	(*a* − *ET*)			
0.5	Rest		80	19	14.5	0.37	0.42	5.3	0.88			113			75			35	31	
1.0	Rest		78	12	8.9	0.19	0.18	2.3	1.06			119			32			41	44	
1.5	Rest		82	13	6.5	0.15	0.20	2.4	0.75			104			39			36	27	
2.0	Rest		85	11	5.6	0.11	0.16	1.9	0.69			107			36			42	29	
2.5	Unloaded		90	34	9.4	0.19	0.34	3.8	0.56			97			41			34	19	
3.0	Unloaded		99	20	9.1	0.21	0.39	3.9	0.54			92			42			35	19	
3.5	Unloaded		93	25	8.1	0.14	0.24	2.6	0.58			90			44			43	25	
4.0	Unloaded		93	20	14.0	0.39	0.62	6.7	0.63			90			43			32	20	
4.5	Unloaded		104	20	13.3	0.35	0.49	4.7	0.71			99			42			33	24	
5.0	Unloaded		98	20	16.9	0.52	0.69	7.0	0.75			101			41			29	22	
5.5	60		118	24	21.1	0.64	0.86	7.3	0.74			100			42			30	22	
6.0	60		122	21	27.3	0.95	1.25	10.2	0.76			99			44			27	20	
6.5	60		123	25	29.8	0.98	1.21	9.8	0.81			104			43			28	23	
7.0	60		128	25	32.9	1.12	1.30	10.2	0.86			105			43			27	24	
7.5	60		125	21	31.4	1.10	1.22	9.8	0.90			107			43			27	24	
8.0	60		129	27	34.9	1.17	1.33	10.3	0.88			108			33			28	25	
8.5	80		124	22	38.7	1.33	1.35	10.9	0.99			108			33			28	27	
9.0	80		133	26	39.7	1.32	1.44	10.8	0.92			108			42			28	26	
9.5	100		138	24	37.5	1.31	1.43	10.4	0.92			107			43			27	25	
10.0	100		138	28	40.1	1.32	1.44	10.4	0.92			108			42			29	26	
10.5	120		151	27	45.3	1.53	1.62	10.7	0.94			110			42			28	27	
11.0	120		154	29	45.4	1.51	1.62	10.5	0.93			110			41			28	27	
11.5	140		159	29	48.5	1.64	1.73	10.9	0.95			108			42			28	27	
12.0	140		160	30	58.0	1.91	2.00	12.5	0.96			104			46			29	28	
12.5	160		165	35	59.4	1.93	2.06	12.5	0.94			112			41			29	27	
13.0	160		168	36	61.0	1.94	2.01	12.0	0.97			111			42			30	29	
13.5	180		174	36	72.9	2.32	2.23	12.8	1.04			114			39			30	31	
14.0	180		177	37	71.3	2.27	2.24	12.7	1.01			115			40			30	30	
14.5	200		187	38	81.7	2.56	2.39	12.8	1.07			117			39			31	33	
15.0	200		189	41	93.8	2.78	2.57	13.6	1.08			119			38			32	35	

Table 10.7.4

Post-β-Adrenergic Blockade

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest		70	20	8.4	0.18	0.23	3.3	0.78			105			40			37	29	
1.0	Rest		70	24	6.6	0.10	0.16	2.3	0.63			105			39			46	29	
1.5	Rest		78	10	14.9	0.44	0.50	6.4	0.88			105			39			32	28	
2.0	Rest		59	16	8.7	0.20	0.23	3.9	0.87			114			36			37	32	
2.5	Unloaded		77	20	9.3	0.26	0.35	4.5	0.74			97			42			29	22	
3.0	Unloaded		85	17	13.7	0.43	0.60	7.1	0.72			94			43			29	20	
3.5	Unloaded		84	16	14.7	0.48	0.62	7.4	0.77			100			43			28	22	
4.0	Unloaded		90	15	9.2	0.27	0.34	3.8	0.79			99			44			29	23	
4.5	Unloaded		90	17	18.7	0.60	0.73	8.1	0.82			94			46			29	24	
5.0	Unloaded		86	19	15.0	0.49	0.59	6.9	0.83			102			42			27	23	
5.5	60		105	19	17.4	0.58	0.76	7.2	0.76			94			47			27	21	
6.0	60		107	17	20.9	0.76	1.03	9.6	0.74			96			44			26	19	
6.5	60		111	24	26.8	0.96	1.26	11.4	0.76			99			44			26	20	
7.0	60		109	22	27.5	1.00	1.15	10.6	0.87			103			45			26	22	
7.5	60		114	20	30.4	1.12	1.24	10.9	0.90			103			45			26	23	
8.0	60		115	25	30.7	1.12	1.28	11.1	0.88			104			44			26	22	
8.5	80		113	23	29.9	1.11	1.22	10.8	0.91			106			44			25	23	
9.0	80		112	22	30.7	1.11	1.20	10.7	0.93			103			46			26	24	
9.5	100		117	21	33.6	1.29	1.34	11.5	0.96			103			47			25	24	
10.0	100		119	26	33.7	1.25	1.37	11.5	0.91			104			45			25	23	
10.5	120		123	23	38.0	1.43	1.45	11.8	0.99			107			44			25	25	
11.0	120		122	25	40.6	1.55	1.63	13.4	0.95			106			45			25	24	
11.5	140		127	28	46.5	1.71	1.71	13.5	1.00			108			44			26	26	
12.0	140		128	28	48.2	1.78	1.77	13.8	1.01			108			46			26	26	
12.5	160		131	27	48.1	1.86	1.84	14.0	1.01			107			45			25	25	
13.0	160		134	31	52.2	1.95	1.93	14.4	1.01			110			44			25	26	
13.5	180		138	31	59.8	2.23	2.06	14.9	1.08			111			44			26	28	
14.0	180		147	32	63.1	2.37	2.13	14.5	1.11			112			43			25	28	
14.5	200		151	35	75.1	2.69	2.26	15.0	1.19			116			42			27	32	
15.0	200		156	41	85.2	2.92	2.39	15.3	1.22			111			42			28	34	

Case 8 Normal Subject: Immediate Effects of Cigarette Smoking

CLINICAL FINDINGS

A 27-year-old subject volunteered for a study to investigate the acute effect of cigarette smoking on cardiovascular and respiratory function during exercise. The subject was apparently in excellent general health, but had smoked cigarettes for 10 years. Physical examination, chest roentgenogram, and ECG were normal.

EXERCISE FINDINGS

Two similar exercise studies were performed 6 days apart on a cycle ergometer. In the 5 hours before the first study, the subject smoked 15 medium-tar cigarettes. In the second study, the subject was under observation for 5 hours without smoking. He breathed supplemental oxygen for the first 3 of those 5 hours to hasten reduction of any carboxyhemoglobin in his blood. On both tests, he pedaled without added load at 60 rpm for 3 minutes. The work rate was then increased 25 W every minute to his symptom-limited maximum. On both occasions, the subject stopped exercise because of fatigue. ECG remained normal. Carboxyhemoglobin levels were 6.1% at the start of the first study and 1.5% at the start of the second study.

INTERPRETATION

Comments

This study is presented because it illustrates the small but significant effects of short-term cigarette smoking on the peak $\dot{V}O_2$ and the anaerobic threshold. It also illustrates the reproducibility of the cardiac and gas exchange responses to exercise performed on different days, and the effects of moderate obesity on the test results.

Resting respiratory function studies (Table 10.8.1) and the resting ECG were normal.

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ was clearly normal without prior smoking but was reduced to a marginally normal level in the setting of prior smoking (Table 10.8.2). The anaerobic threshold was reduced after smoking but was normal without prior smoking (Table 10.8.2). Referring to Flowchart 2 (Fig. 8.2), the subject is 20% overweight (branch point 2.2 of Fig. 8.2). This obese subject's $\dot{V}O_2$ during unloaded cycling was approximately 0.95 L/min (Table 10.8.3 and panel 1 of Figs. 10.8.1 and 10.8.2).

Table 10.8.1

Selected Respiratory Function Data

Measurement	Predicted	With prior smoking	Without smoking
Age (years)		27	27
Sex		Male	Male
Height (cm)		168	168
Weight (kg)	69	83	83
Hematocrit (%)		47	47
VC (L)	4.65	4.18	4.20
IC (L)	3.10	3.43	3.43
TLC (L)	6.19	6.26	6.68
FEV_1 (L)	3.79	3.57	3.55
FEV_1/VC (%)	81	85	85
MVV (L/min)	168	149	163
DLCO (mL/mm Hg/min)	31.2	34.7	37.4

Table 10.8.2

Selected Exercise Data

Measurement	Predicted	With prior smoking	Without smoking
Peak $\dot{V}O_2$ (L/min)	2.99	2.55	2.73
Maximum heart rate (beats/min)	193	178	182
Maximum O_2 pulse (mL/beat)	15.5	14.3	15.0
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	9.0	9.9
AT (L/min)	>1.23	1.1	1.25
Blood pressure (mm Hg [rest, max])		138/84, 183/110	132/84, 186/105
Maximum $\dot{V}E$ (L/min)		110	121
Exercise breathing reserve (L/min)	>15	39	42
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	24.8	24.6	24.3
PaO_2 (mm Hg [rest, max ex])		102, 103	109, 106
$P(A-a)O_2$ (mm Hg [rest, max ex])		5, 19	–1, 16
$PaCO_2$ (mm Hg [rest, max ex])		39, 34	39, 34
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		–1, –3	–2, –3
V_D/V_T (rest, heavy ex)		0.37, 0.18	0.27, 0.20
HCO_3^- (mEq/L [rest, 2-min recov])		25, 14	26, 15
COHb (%)	<2	6.1	1.5

Indices other than peak $\dot{V}O_2$ and *AT* that might reflect the effect of the increased carboxyhemoglobin during exercise are the O_2 pulse and $\Delta\dot{V}O_2/\Delta WR$. These are both reduced after cigarette smoking compared to before, although still within normal limits (Table 10.8.2). Although the indices of ventilation–perfusion matching ($P[ET-a]CO_2$ and V_D/V_T) are normal at maximum exercise in this and most normal subjects, there is a trend toward abnormality immediately after smoking (Tables 10.8.3 and 10.8.4).

Conclusion

Cigarette smoking and obesity have affected exercise performance in an otherwise normal subject.

Table 10.8.3

With Prior Smoking

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	138/84								7.42	24		98			38				
0.5	Rest		76	26	12.1	0.24	0.31	4.1	0.77			100			41			41	32	
1.0	Rest		77	27	13.4	0.27	0.31	4.0	0.87			106			39			41	36	
1.5	Rest		76	27	11.1	0.21	0.27	3.6	0.78			97			42			42	33	
2.0	Rest	138/84	77	25	13.2	0.28	0.32	4.2	0.88	7.42	25	107	102	5	40	39	–1	40	35	0.37
2.5	Rest		76	25	12.4	0.26	0.30	3.9	0.87			105			40			40	34	
3.0	Rest		75	25	11.7	0.23	0.26	3.5	0.88			104			41			42	37	
3.5	Unloaded		99	19	15.8	0.50	0.51	5.2	0.98			104			43			28	2	8
4.0	Unloaded		101	20	17.1	0.56	0.65	6.4	0.86			97			43			28	24	
4.5	Unloaded		103	21	19.2	0.69	0.89	8.6	0.78			93			46			25	20	
5.0	Unloaded		103	21	23.6	0.87	0.96	9.3	0.91			97			45			25	23	
5.5	Unloaded		102	24	21.8	0.76	0.84	8.2	0.90			100			45			26	24	
6.0	Unloaded	156/96	105	23	23.8	0.85	0.92	8.8	0.92	7.39	24	102	98	8	45	41	–4	26	24	0.17
6.5	25		107	22	22.5	0.81	0.89	8.3	0.91			99			45			25	23	
7.0	25		109	21	24.0	0.90	0.99	9.1	0.91			100			44			25	22	
7.5	50		113	25	27.0	0.97	1.03	9.1	0.94			99			46			26	24	
8.0	50	165/93	115	23	32.1	1.16	1.17	10.2	0.99	7.38	24	101	95	13	45	41	–3	26	26	0.20
8.5	75		123	25	31.6	1.20	1.24	10.1	0.97			100			46			25	24	
9.0	75		124	25	35.4	1.36	1.33	10.7	1.02			103			46			24	25	
9.5	100		129	27	36.8	1.42	1.38	10.7	1.03			102			47			24	25	
10.0	100	177/96	135	26	43.4	1.68	1.53	11.3	1.10	7.36	24	102	94	16	47	43	–4	25	27	0.17
10.5	125		145	29	43.0	1.70	1.61	11.1	1.06			103			47			24	25	
11.0	125		150	30	50.8	2.01	1.88	12.5	1.07			103			48			24	26	
11.5	150		154	33	57.5	2.21	1.99	12.9	1.11			105			47			25	27	
12.0	150	177/99	162	36	66.6	2.47	2.09	12.9	1.18	7.33	22	107	95	18	46	42	–4	26	30	0.19
12.5	175		171	36	70.4	2.66	2.24	13.1	1.19			108			46			25	30	
13.0	175		172	43	84.8	2.95	2.34	13.6	1.26			112			43			28	35	
13.5	200		176	51	101.2	3.27	2.51	14.3	1.30			115			41			30	39	
14.0	200		178	62	110.6	3.36	2.55	14.3	1.32	7.32	17	119	103	19	37	34	–3	31	41	0.18
14.5	Recovery		176	45	95.2	2.99	2.18	12.4	1.37			119			39			31	42	
15.0	Recovery		164	43	81.4	2.46	1.49	9.1	1.65			123			37			32	52	
15.5	Recovery		160	43	70.6	1.93	1.15	7.2	1.68			125			36			35	58	
16.0	Recovery	165/84	153	35	53.3	1.46	0.98	6.4	1.49	7.27	14	123	112	14	35	32	–3	34	51	0.21

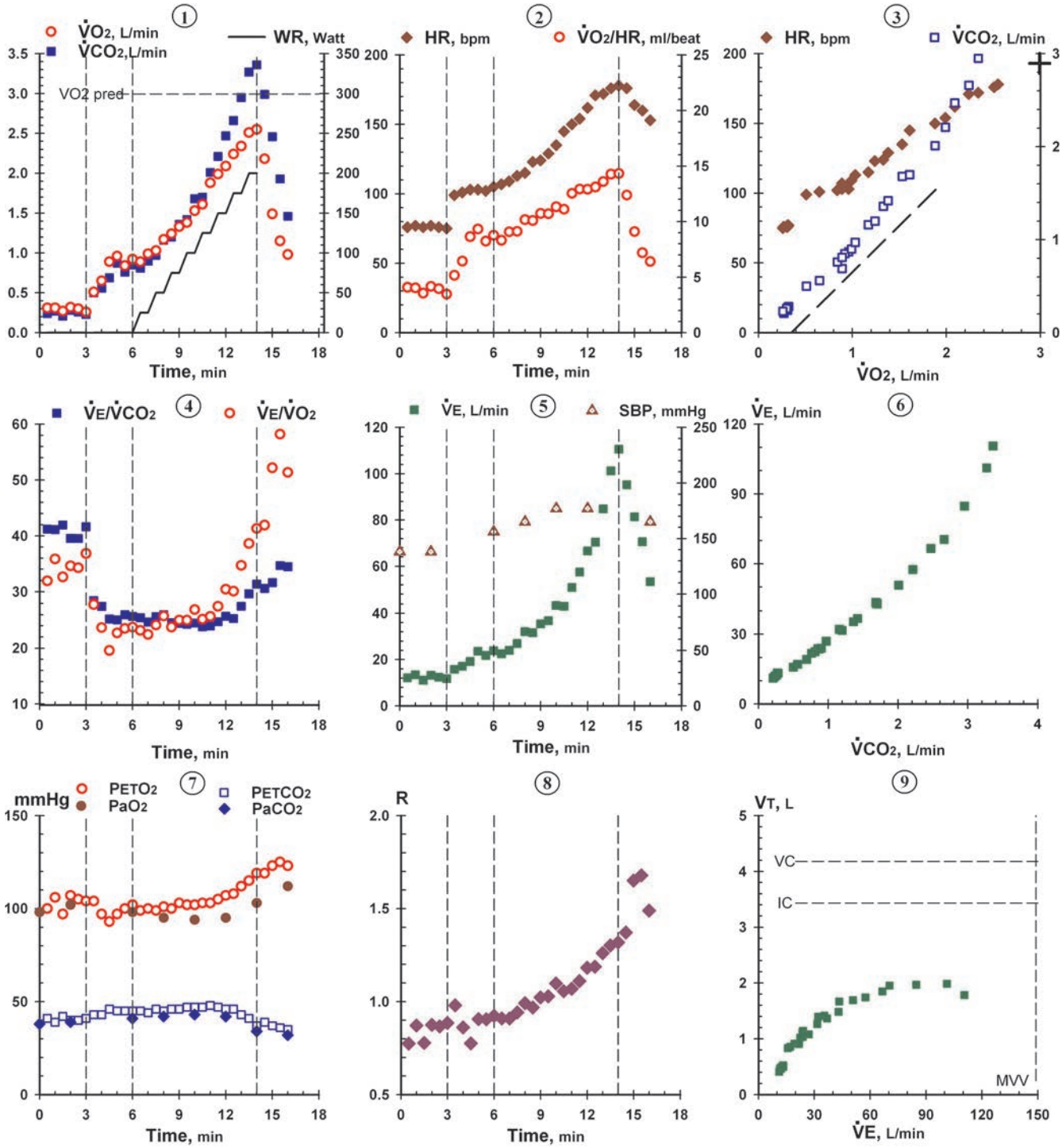

FIGURE 10.8.1. With prior cigarette smoking. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 25 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

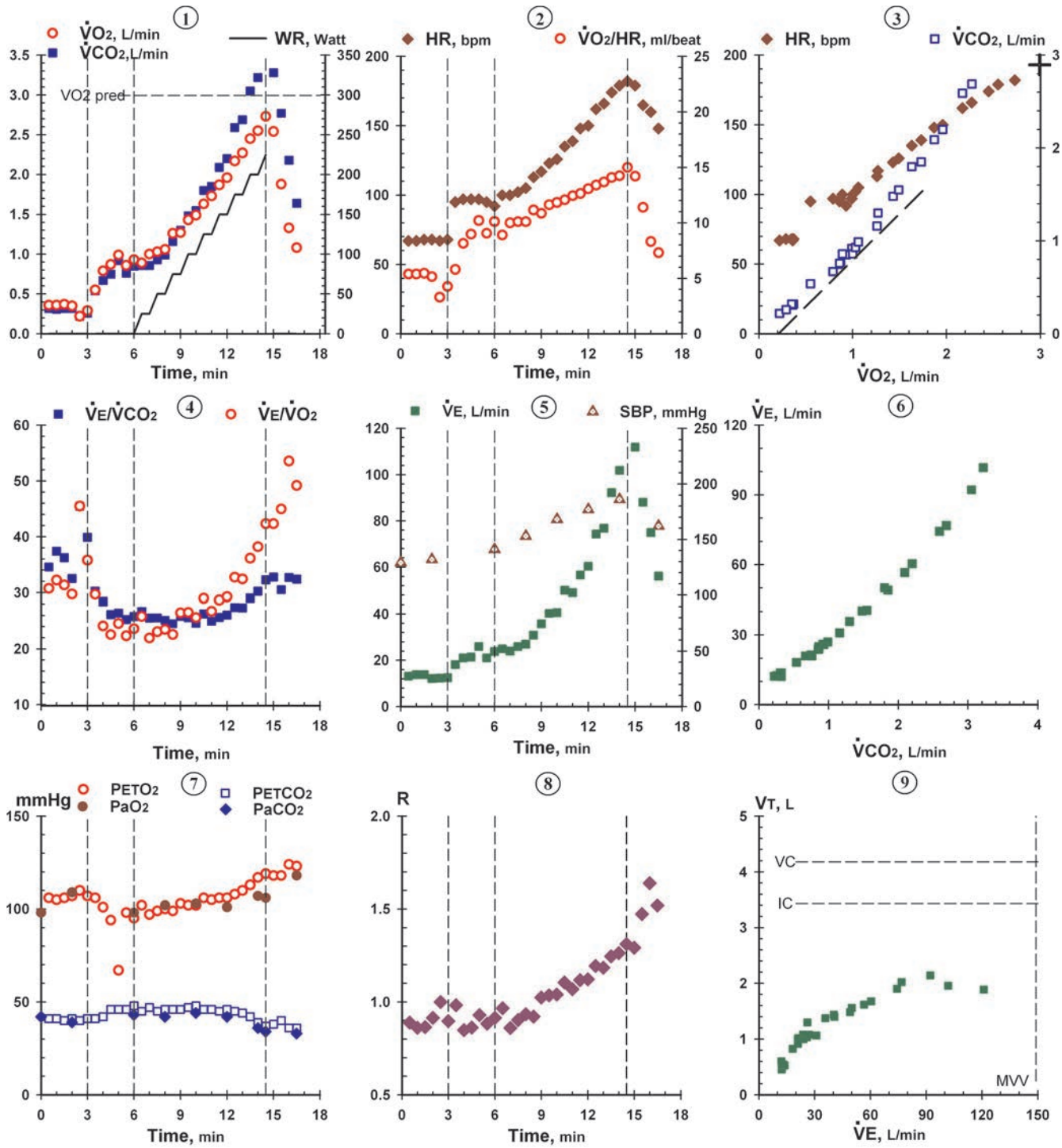

FIGURE 10.8.2. Without prior cigarette smoking. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 25 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $P_{ET}CO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.8.4

Without Prior Smoking

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	129/84								7.40	26		99			42				
0.5	Rest		67	24	13.1	0.32	0.36	5.4	0.89			106			41			35	31	
1.0	Rest		67	26	13.8	0.31	0.36	5.4	0.86			105			41			37	32	
1.5	Rest		68	26	13.8	0.32	0.37	5.4	0.86			106			40			36	31	
2.0	Rest	132/84	68	20	12.1	0.32	0.35	5.1	0.91	7.43	25	107	109	–1	41	39	–2	33	30	0.27
2.5	Rest		67	27	12.3	0.22	0.22	3.3	1.00			110			40			45	45	
3.0	Rest		68	25	12.5	0.26	0.29	4.3	0.9			107			41			40	36	
3.5	Unloaded		95	22	18.2	0.54	0.55	5.8	0.98			106			41			30	30	
4.0	Unloaded		97	23	21.0	0.67	0.79	8.1	0.85			101			42			28	24	
4.5	Unloaded		97	21	21.4	0.75	0.87	9.0	0.86			94			46			26	23	
5.0	Unloaded		97	20	26.0	0.92	0.99	10.2	0.93			67			46			26	25	
5.5	Unloaded		95	21	21.0	0.76	0.86	9.1	0.88			98			46			25	22	
6.0	Unloaded	141/87	92	22	23.8	0.85	0.93	10.1	0.91	7.39	26	95	98	6	48	43	–5	26	24	0.20
6.5	25		100	24	25.0	0.86	0.89	8.9	0.97			102			45			27	26	
7.0	25		100	24	24.0	0.86	1.00	10.0	0.86			97			47			26	22	
7.5	50		102	25	25.9	0.93	1.03	10.1	0.90			99			45			26	23	
8.0	50	153/90	105	25	27.0	0.99	1.06	10.1	0.93	7.39	25	100	102	4	46	42	–4	25	23	0.17
8.5	75		113	29	30.9	1.16	1.26	11.2	0.92			99			46			25	23	
9.0	75		117	26	35.8	1.30	1.27	10.9	1.02			103			46			26	26	
9.5	100		123	28	40.3	1.48	1.43	11.6	1.03			102			47			26	27	
10.0	100	168/93	126	29	40.6	1.55	1.49	11.8	1.04	7.37	25	102	103	4	48	44	–4	25	26	0.19
10.5	125		135	32	50.0	1.80	1.63	12.1	1.10			106			46			26	29	
11.0	125		139	33	49.0	1.85	1.73	12.4	1.07			105			46			25	27	
11.5	150		148	35	56.6	2.09	1.87	12.6	1.12			106			45			26	29	
12.0	150	177/99	150	36	60.4	2.20	1.96	13.1	1.12	7.36	23	106	101	11	46	42	–4	26	29	0.20
12.5	175		162	39	74.3	2.59	2.17	13.4	1.19			108			45			27	33	
13.0	175		166	38	76.8	2.69	2.27	13.7	1.19			110			44			27	32	
13.5	200		174	43	92.2	3.05	2.45	14.1	1.24			113			42			29	36	
14.0	200	186/105	179	52	101.8	3.22	2.55	14.2	1.26	7.35	20	117	107	13	39	36	–3	30	38	0.20
14.5	225		182	64	121.0	3.58	2.73	15.0	1.31	7.32	17	119	106	16	37	34	–3	32	42	0.20
15.0	Recovery		179	52	111.9	3.28	2.54	14.2	1.29			118			38			33	42	
15.5	Recovery	165		41	88.0	2.77	1.88	11.4	1.47			118			40			31	45	
16.0	Recovery		160	43	74.9	2.18	1.33	8.3	1.64			124			36			33	54	
16.5	Recovery	162/90	148	35	56.1	1.64	1.08	7.3	1.52	7.26	15	123	118	8	36	33	–3	32	49	0.18

Case 9 Active Normal Man with Suspected Cardiac Disease

CLINICAL FINDINGS

A 65-year-old self-employed male executive had cardiopulmonary exercise testing to evaluate exertional dyspnea that he had experienced when hiking at an altitude of 10,000 ft (3 km). He had been an avid hiker for years but had noted a decreased ability to hike at high altitudes over the last 3 to 4 years. Of note, he was accustomed to taking the lead on hiking trips even as he aged and became progressively older compared to other hikers on the outings. He was referred to a cardiologist, who performed an extensive workup, including treadmill exercise tests (without gas exchange measurements), a nuclear medicine cardiac scan, echocardiogram, and coronary angiogram. The results of these tests were negative, but he was nevertheless told that he probably had an occult cardiomyopathy and was prescribed an angiotensin-converting enzyme inhibitor. The patient referred himself for a cardiopulmonary exercise test because he believed that the drug did not help him. Pulmonary function was normal (Table 10.9.1).

EXERCISE FINDINGS

Because his symptoms were limited to when he was hiking at altitude, the patient performed exercise on a cycle ergometer, first while breathing room air, and then while breathing 15% O_2 (equivalent to an 8,000-ft altitude). On both occasions, he pedaled at 60 rpm without an added load for 3 minutes, followed by an increase in work rate by 20 W per minute to tolerance. Arterial blood was sampled every second minute, and intra-arterial pressure was recorded from a percutaneously placed brachial artery catheter (Tables 10.9.2, 10.9.3, and 10.9.4 and Figs. 10.9.1 and 10.9.2). The patient stopped exercise because of fatigue and shortness of breath. No ECG abnormalities were noted at rest or during exercise.

Table 10.9.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		65
Sex		Male
Height (cm)		183
Weight (kg)	83	83
Hematocrit (%)		44
VC (L)	4.60	4.70
IC (L)	3.06	3.70
FEV_1 (L)	3.45	3.47
FEV_1/VC (%)	75	74
MVV (L/min)	142	129
DLCO (mL/mm Hg/min)	28.0	28.6

Table 10.9.2

Selected Exercise Data

Measurement	Predicted (room air)	Measured	
		Air	15% O_2
Peak $\dot{V}O_2$ (L/min)	2.21	2.69	2.19
Maximum heart rate (beats/min)	155	175	172
Maximum O_2 pulse (mL/beat)	14.3	15.9	12.9
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.3	10.3	7.8
AT (L/min)	>0.99	1.9	1.2
Blood pressure (mm Hg [rest, max])		132/72, 210/90	114/66, 198/96
Maximum $\dot{V}E$ (L/min)		115	108
Exercise breathing reserve (L/min)	>15	14	21
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.2	30.2	29.9
PaO_2 (mm Hg [rest, max ex])		113, 106	77, 52
$P(A-a)O_2$ (mm Hg [rest, max ex])		–1, 16	0, 27
$PaCO_2$ (mm Hg [rest, max ex])		35, 33	32, 32
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		1, –3	2, 0
VD/VT (rest, heavy ex)		0.25, 0.21	0.36, 0.19
HCO_3^- (mEq/L [rest, 2-min recov])		21, 15	21, 17

Table 10.9.3

Room Air

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0.5	Rest		68	24	15.6	0.33	0.31	4.6	1.06			119			30			41	44	
1.0	Rest		68	16	17.5	0.40	0.33	4.9	1.21			119			30			40	49	
1.5	Rest		77	17	14.4	0.31	0.27	3.5	1.15			118			31			42	48	
2.0	Rest		83	22	17.8	0.39	0.33	4.0	1.18			114			32			41	48	
2.5	Unloaded		83	19	19.9	0.53	0.55	6.6	0.96			113			33			35	33	
3.0	Unloaded		80	21	21.3	0.53	0.49	6.1	1.08			115			32			37	40	
3.5	Unloaded		80	19	19.9	0.55	0.52	6.5	1.06			111			34			33	35	
4.0	Unloaded		76	19	21.2	0.58	0.63	8.3	0.92			112			33			34	31	
4.5	Unloaded		75	19	21.0	0.55	0.58	7.7	0.95			113			33			35	33	
5.0	Unloaded	135/72	81	23	19.8	0.52	0.58	7.2	0.90	7.40	21	110	113	–1	34	35	–1	34	31	0.25
5.5	20		81	18	24.5	0.67	0.65	8.0	1.03			109			34			34	35	
6.0	20		85	20	22.8	0.63	0.71	8.4	0.89			111			34			33	30	
6.5	40		87	21	27.1	0.81	0.85	9.8	0.95			105			33			31	30	
7.0	40	144/75	88	19	25.1	0.75	0.79	9.0	0.95	7.40	21	111	120	–6	36	35	–1	31	30	0.20
7.5	60		98	19	28.0	0.81	0.87	8.9	0.93			112			34			33	30	
8.0	60		100	20	29.4	0.91	1.10	11.0	0.83			107			35			30	25	
8.5	80		99	21	33.7	1.04	1.24	12.5	0.84			108			36			31	26	
9.0	80	144/75	112	21	34.5	1.07	1.23	11.0	0.87	7.40	21	108	106	5	36	35	–1	31	27	0.18
9.5	100		110	23	33.3	1.20	1.39	12.6	0.86			109			36			26	23	
10.0	100	162/84	113	23	42.6	1.33	1.50	13.3	0.89	7.40	22	110	109	1	35	36	–1	31	27	0.21
10.5	120		120	25	45.6	1.43	1.57	13.1	0.91			109			36			30	28	
11.0	120	168/84	124	24	49.6	1.57	1.69	13.6	0.93	7.40	23	110	107	4	36	37	1	30	28	0.22
11.5	140		130	24	51.2	1.67	1.84	14.2	0.91			108			37			29	27	
12.0	140		135	27	59.8	1.81	1.99	14.7	0.91			111			36			32	29	
12.5	160		140	29	61.2	1.87	2.03	14.5	0.92			109			38			31	29	
13.0	160	174/84	149	32	66.7	2.14	2.18	14.6	0.98	7.40	21	113	107	–7	36	35	–1	30	29	0.17
13.5	180		152	27	64.3	2.12	2.14	14.1	0.99			108			39			29	29	
14.0	180		154	31	73.7	2.45	2.45	15.9	1.00			112			37			29	29	
14.5	200		160	33	78.7	2.61	2.54	15.9	1.03			110			38			29	30	
15.0	200	207/84	172	36	91.8	2.91	2.60	15.1	1.12	7.40	21	117	100	18	35	35	0	30	34	0.19
15.5	220		175	42	102.1	3.09	2.69	15.4	1.15			118			34			32	37	
16.0	220	210/90	174	49	115.3	3.25	2.69	15.5	1.21	7.40	20	121	106	15	32	33	–1	34	41	0.23
16.5	Recovery		162	34	92.9	2.94	2.24	13.8	1.31	7.30	16	119	107	16	36	33	–3	31	40	0.14
17.0	Recovery		154	36	87.3	2.44	1.58	10.3	1.54			125			32			35	53	
17.5	Recovery		140	29	62.8	1.73	1.07	7.6	1.62			127			32			35	56	
18.0	Recovery		125	24	49.1	1.39	0.89	7.1	1.56	7.30	15	125	132	–4	33	31	–2	34	53	0.17

INTERPRETATION

Comments

Resting respiratory function studies were normal.

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ and *AT* are both normal, well above predicted values for sedentary men. Proceeding to Flowchart 2 (Fig. 8.2) through branch points 2.1 and 2.2, it is apparent that the patient is an exceptionally fit man. The low breathing reserve is compatible with high cardiovascular capacity and good motivation. While the patient was breathing 15% O_2, PaO_2 was reduced due to the lower FIO_2 and decreased further with exercise. Peak $\dot{V}O_2$, peak O_2 pulse, and *AT* all decreased relative to the room air study. These decreases were expected because all of these measurements are O_2 transport-dependent. $\Delta\dot{V}O_2/\Delta WR$ was also somewhat reduced.

Conclusion

This man had excellent cardiovascular function with no evidence to support the diagnosis of cardiomyopathy. His symptoms were most likely due to the decrease in cardiovascular function associated with aging, which were highlighted when he tried to continue his physical feats of earlier years at the pace of younger colleagues.

Table 10.9.4

15% Oxygen

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest		73	17	12.7	0.24	0.22	3.0	1.08			81			28			47	51	
1.0	Rest		67	14	12.1	0.30	0.28	4.2	1.07			78			31			36	39	
1.5	Rest		69	14	13.9	0.32	0.32	4.6	1.00			76			31			40	40	
2.0	Rest	114/56	67	15	9.1	0.17	0.16	2.4	1.07	7.44	21	79	77	0	30	32	–2	46	49	0.36
2.5	Rest		66	11	16.0	0.42	0.37	5.5	1.15			80			31			36	41	
3.0	Rest		75	16	10.3	0.17	0.15	2.0	1.16			82			29			53	61	
3.5	Unloaded		76	19	15.8	0.37	0.31	4.0	1.20			82			30			38	46	
4.0	Unloaded		81	14	17.5	0.48	0.45	5.6	1.07			76			33			34	36	
4.5	Unloaded		82	19	23.1	0.63	0.59	7.2	1.07			76			33			34	36	
5.0	Unloaded		84	15	18.4	0.53	0.54	6.5	0.97			72			34			32	31	
5.5	Unloaded		79	17	20.8	0.59	0.59	7.5	1.00			73			34			33	33	
6.0	Unloaded	132/36	73	15	19.8	0.55	0.51	7.1	1.07	7.39	20	77	76	0	32	33	1	34	36	0.21
6.5	20		84	22	15.7	0.45	0.46	5.5	0.97			70			36			31	30	
7.0	20		85	18	22.2	0.64	0.64	7.5	1.00			73			34			32	32	
7.5	40		85	18	23.6	0.73	0.73	8.6	1.00			72			35			30	30	
8.0	40	114/60	92	16	24.2	0.75	0.75	8.1	1.00	7.41	22	72	68	4	35	35	0	30	30	0.18
8.5	60		95	18	26.8	0.81	0.81	8.5	1.00			72			35			31	31	
9.0	60		102	22	29.4	0.89	0.86	8.5	1.03			72			36			31	32	
9.5	80		105	19	33.0	1.04	0.98	9.3	1.06			73			36			30	32	
10.0	80	144/66	105	22	36.0	1.11	1.01	9.7	1.10	7.42	22	75	66	9	35	35	0	31	34	0.19
10.5	100		108	23	38.9	1.20	1.10	10.1	1.10			75			35			31	34	
11.0	100		115	22	41.5	1.30	1.19	10.3	1.10			75			35			30	33	
11.5	120		114	24	45.7	1.43	1.23	10.8	1.16			76			36			31	36	
12.0	120	144/66	124	25	49.2	1.53	1.40	11.3	1.10	7.42	22	75	60	15	35	34	–1	31	34	0.17
12.5	140		124	28	54.5	1.65	1.45	11.7	1.14			77			34			32	36	
13.0	140		129	28	59.4	1.80	1.49	11.5	1.21			78			35			32	38	
13.5	160		140	28	65.7	2.00	1.71	12.2	1.17			77			35			32	37	
14.0	160	174/73	148	30	72.0	2.15	1.77	11.9	1.22	7.41	21	79	57	21	34	34	0	32	39	0.21
14.5	180		150	30	73.6	2.21	1.88	12.5	1.17			78			34			32	38	
15.0	180		152	28	74.6	2.29	1.83	12.0	1.25			79			35			32	39	
15.5	200		152	28	75.6	2.36	1.88	12.4	1.25			79			35			31	39	
16.0	200	195/84	160	33	84.8	2.57	1.98	12.4	1.30	7.38	19	80	52	28	35	33	–2	32	41	0.17
16.5	220		170	44	101.6	2.78	2.19	12.9	1.27			81			33			35	45	
17.0	220	198/96	172	45	107.9	3.03	2.15	12.5	1.41	7.33	17	85	56	27	31	32	1	34	49	0.21
17.5	Recovery		172	41	97.3	2.77	1.93	11.2	1.44			84			33			34	49	
18.0	Recovery		154									91			33					

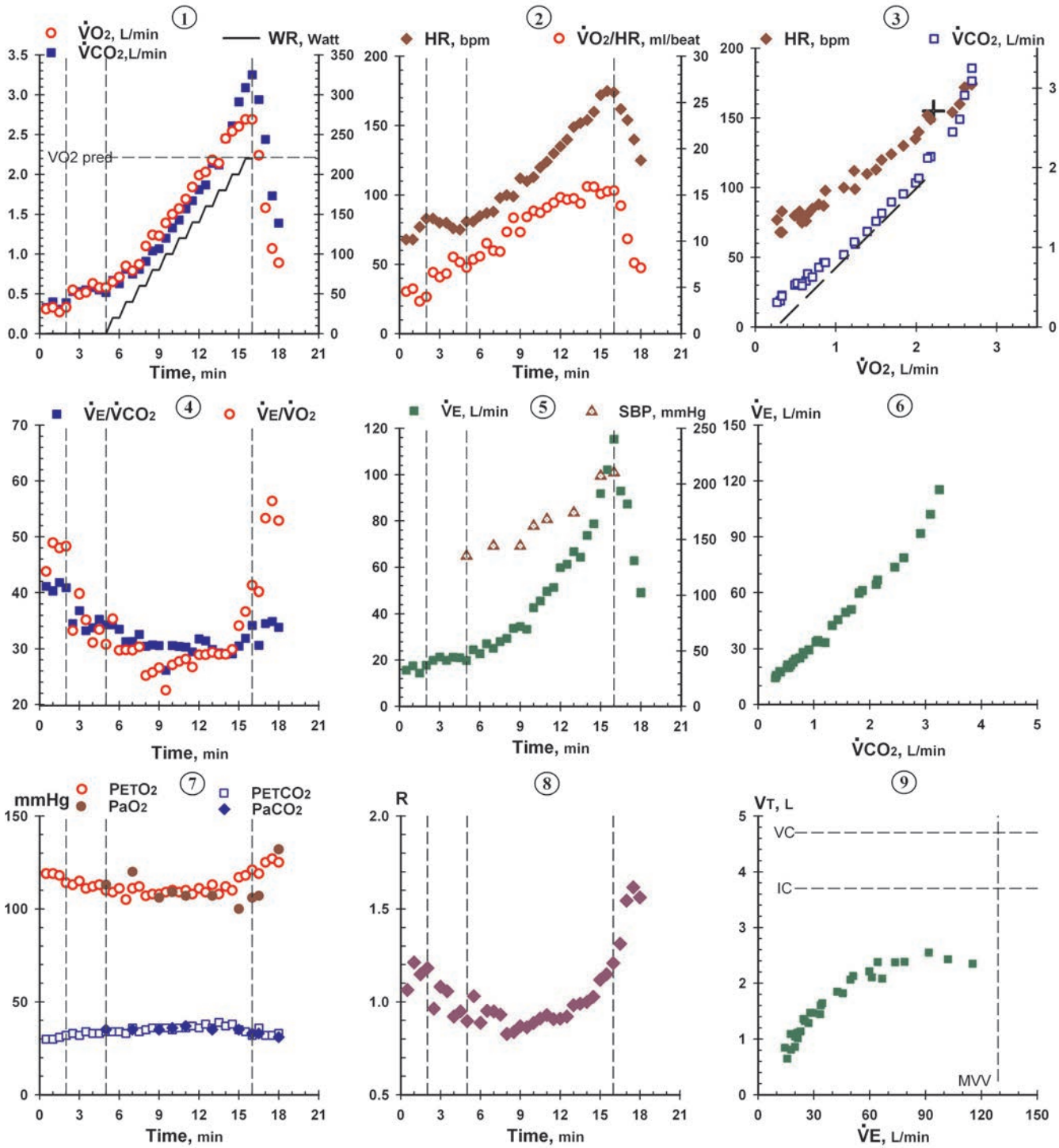

FIGURE 10.9.1. Air breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

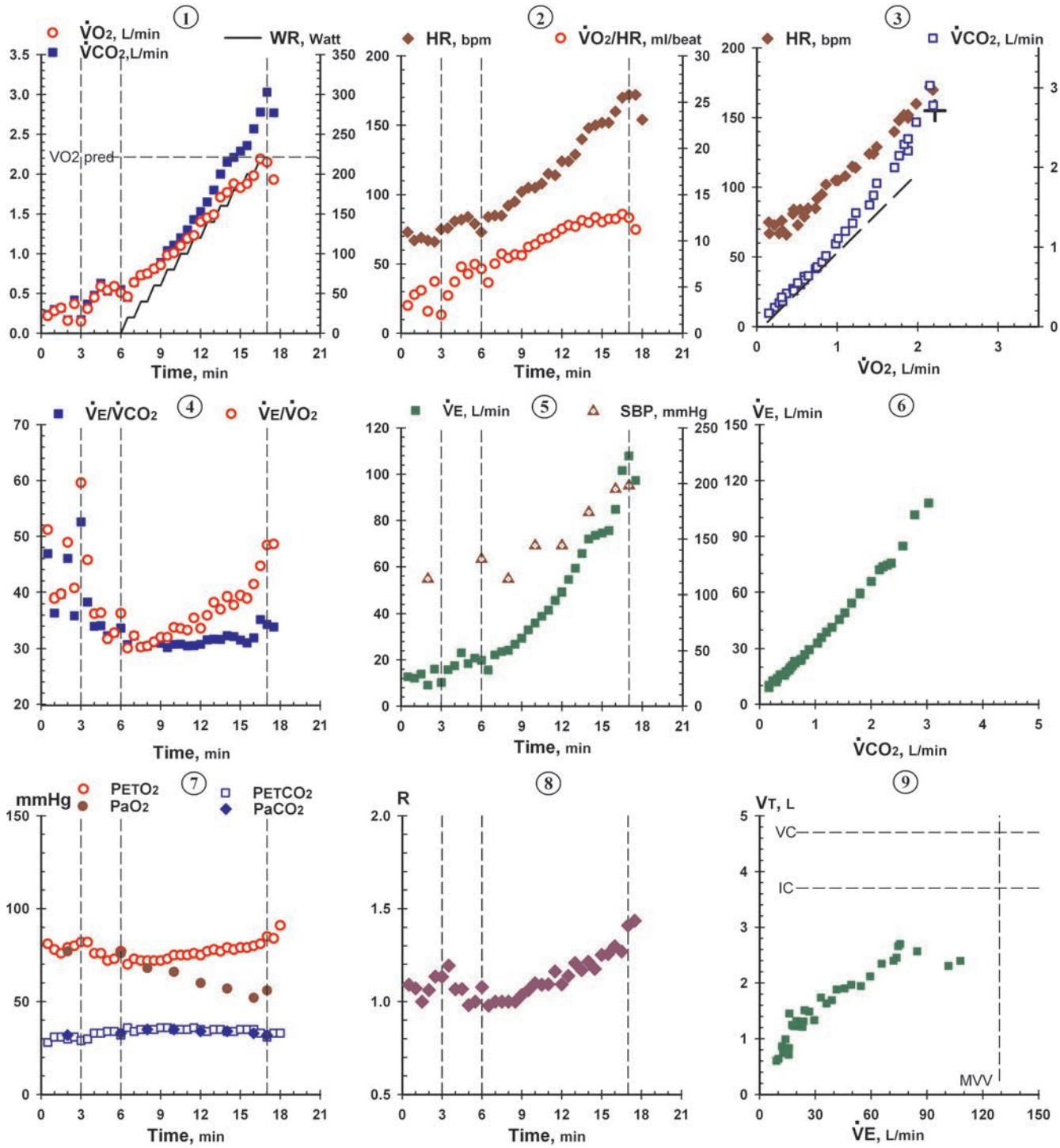

FIGURE 10.9.2. 15% oxygen breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 10 Normal Sedentary Woman

CLINICAL FINDINGS

A retired health care professional was referred for exercise testing because she had become fatigued and short of breath when trying to keep pace with others on a recent sightseeing tour, despite apparently good control of her asthma. She lived by herself and reported that she did her own housekeeping, but did not do any other regular physical activity. On examination, her lungs were clear to auscultation. Cardiac examination was unremarkable and extremities were free of edema. She took inhaled medications for asthma and an antidepressant. Routine blood work, including blood counts and thyroid function tests, had been normal and the resting ECG was normal. Resting respiratory function was normal (Table 10.10.1).

EXERCISE FINDINGS

The patient exercised on a cycle ergometer. She pedaled at 60 rpm without added resistance for 2 minutes, after which the work rate was increased continuously at a rate of 10 W per minute until she stopped with generalized fatigue as the limiting symptom. ECG showed no ischemic changes and the patient had no chest tightness or wheezing.

Table 10.10.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		75
Sex		Female
Height (cm)		149
Weight (kg)		57
VC (L)	1.88	2.48
IC (L)	1.26	2.21
FEV_1 (L)	1.43	1.88
FEV_1/VC (%)	79	81
MVV (L/min)	61	63
DLCO (mL/mm Hg/min)	15.95	16.01

Table 10.10.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	0.89	0.92
Maximum heart rate (beats/min)	145	116
Maximum O_2 pulse (mL/beat)	6.1	8.0
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.6
AT (L/min)	>0.51	0.52
Blood pressure (mm Hg [rest, max])		131/65, 172/82
Maximum $\dot{V}E$ (L/min)		37
Exercise breathing reserve (L/min)	>15	26
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	31.6	37.8

Analysis

Peak $\dot{V}O_2$ was normal and anaerobic threshold was near the lower limit of normal (Tables 10.10.2 and 10.10.3). Breathing reserve was adequate, there was no apparent arterial desaturation, and ventilatory requirements relative to metabolic rate were not excessive (panels 4, 7, 9 in Fig. 10.10.1). The test was interpreted as showing an attenuated heart rate response and marginal anaerobic threshold. Because maximal exercise capacity was normal and there were no clear pathologic findings, it was concluded that the patient's exercise capacity was consistent with her age and activity pattern. Although the patient's *AT* was within the normal reference range, the metabolic demands of many common ambulatory activities are higher than the patient's value, so it could be expected that the patient would find them to be nonsustainable and fatiguing.

Conclusion

This patient's exercise capacity reflects the compound effects of aging and inactivity on cardiovascular fitness and muscle mass and function.

Table 10.10.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.0	Rest	131/65	67	14	6.4	0.14	0.18	2.7	0.74			104			36			47	35	
0.5	Rest		67	15	6.6	0.15	0.21	3.2	0.72			103			36			43	31	
1.0	Unloaded	131/65	77	15	9.0	0.24	0.34	4.4	0.70			98			38			38	27	
1.5	Unloaded		79	17	12.1	0.29	0.36	4.5	0.80			105			36			42	34	
2.0	Unloaded		77	12	10.0	0.28	0.35	4.5	0.79			103			38			36	29	
2.5	Unloaded		82	19	11.6	0.30	0.37	4.4	0.81			103			38			39	32	
3.0	0	131/65	86	15	13.7	0.38	0.46	5.3	0.84			104			39			36	30	
3.5	5		83	18	13.2	0.36	0.40	4.8	0.89			106			38			37	33	
4.0	10		83	19	14.5	0.39	0.44	5.3	0.88			106			38			37	33	
4.5	15		83	20	15.2	0.40	0.43	5.2	0.92			109			36			38	35	
5.0	20		88	22	17.5	0.46	0.52	5.9	0.88			107			37			38	34	
5.5	25		90	20	19.9	0.53	0.54	6.0	0.98			111			36			38	37	
6.0	30		92	19	21.1	0.55	0.55	6.0	0.99			111			36			38	38	
6.5	35		98	21	20.0	0.55	0.59	6.0	0.94			108			38			36	34	
7.0	40	172/82	102	24	26.1	0.69	0.66	6.4	1.05			112			36			38	40	
7.5	45		104	27	26.8	0.71	0.70	6.7	1.02			111			37			38	39	
8.0	50		105	30	31.7	0.78	0.70	6.7	1.11			115			35			41	45	
8.5	55		110	29	32.0	0.81	0.79	7.2	1.03			113			35			39	40	
9.0	60		112	28	32.0	0.86	0.82	7.3	1.04			112			37			37	39	
9.5	65		116	31	37.2	0.99	0.92	7.9	1.08			114			35			38	41	
10.0	Recovery	172/82	104	24	25.4	0.75	0.76	7.3	0.98			109			39			34	33	
10.5	Recovery		92	22	25.8	0.76	0.74	8.0	1.03			109			39			34	35	
11.0	Recovery	147/64	84	23	21.8	0.58	0.49	5.8	1.18			116			36			38	45	
11.5	Recovery		82	22	22.1	0.53	0.42	5.2	1.24			119			34			42	52	

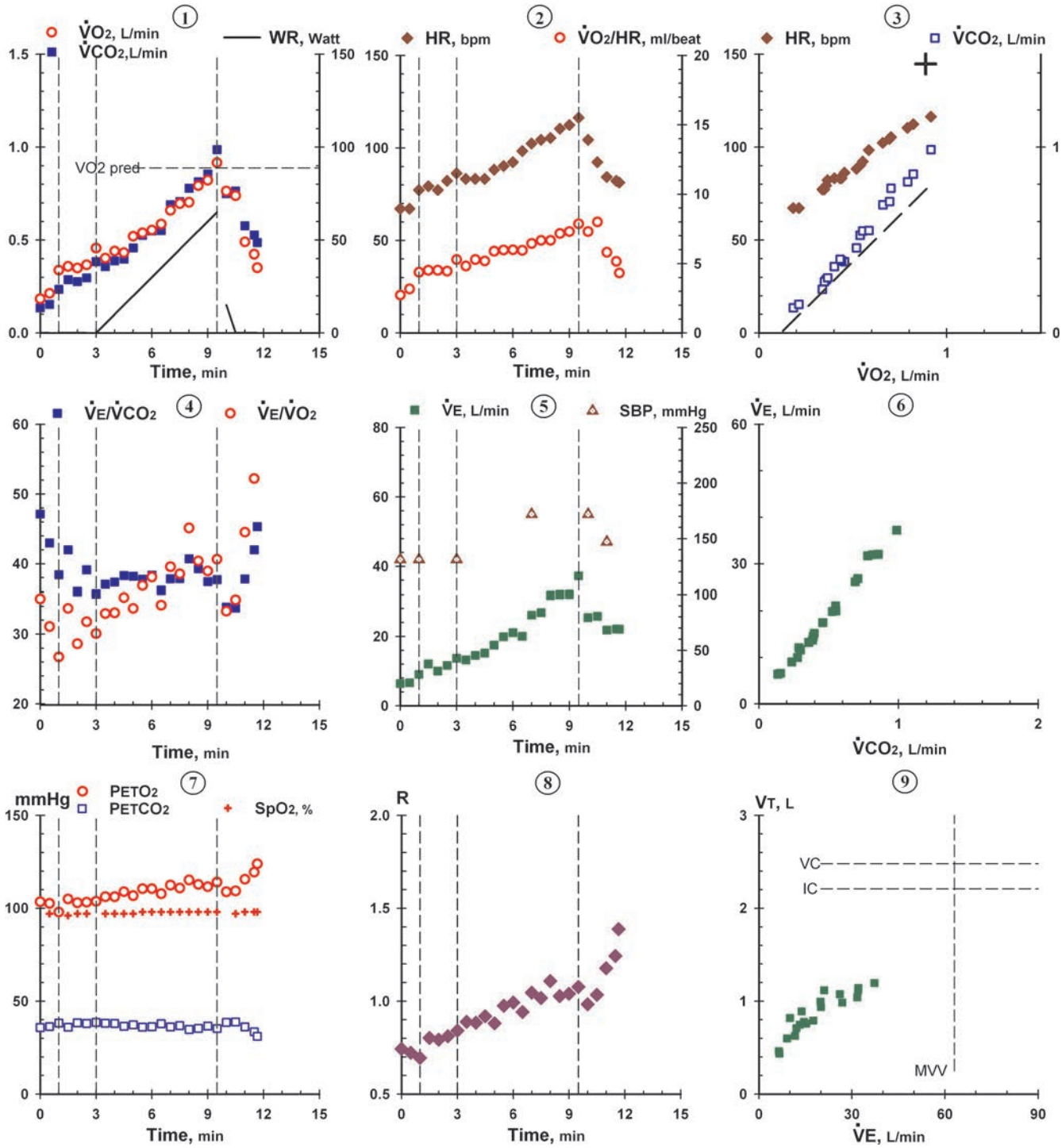

FIGURE 10.10.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 11 Normal Aging Athletic Man

CLINICAL FINDINGS

At age 66, a man with treated hypertension and asthma engaged in vigorous exercise and was referred for exercise testing by his physician to exclude silent myocardial ischemia. Over the next decade, he maintained a regular exercise training regimen and returned periodically for repeat testing. On each testing occasion, his physical examination was unremarkable. His medications included an angiotensin-converting enzyme inhibitor, diuretic, and inhaled asthma medications. Data from tests performed at ages 66 and 76 illustrate effects of aging on exercise capacity of a healthy individual who maintains a high level of physical training, and also as an example of the remarkable similarity of exercise response patterns in a given individual over time when the individual's clinical condition is stable.

Table 10.11.1

Selected Respiratory Function Data

Measurement	Predicted	Measured	Predicted	Measured
Age (years)		66		76
Sex		Male		Male
Height (cm)		171		172
Weight (kg)		81		72
VC (L)	3.72	4.10	3.81	4.21
IC (L)	2.48	3.69	3.07	2.99
FEV_1 (L)	2.96	2.32	2.74	2.41
FEV_1/VC (%)	80	57	72	57
MVV (L/min)	124	128	112	131

EXERCISE FINDINGS

On both tests, exercise was performed on a cycle ergometer beginning with 3 minutes of rest and 3 minutes of unloaded cycling, followed by progressive increase in work rate by 20 W per minute. He ended the tests because of leg fatigue.

Comments

Pulmonary function tests (Table 10.11.1) showed an above-average VC with mild to moderate expiratory airflow obstruction.

Analysis

At age 66, peak $\dot{V}O_2$ and anaerobic threshold were above the age-based predicted normal values (Tables 10.11.2 and 10.11.3 and Fig. 10.11.1). The peak heart rate was very close to the age-based predicted value, so the peak oxygen pulse was high. This is consistent with an increased stroke volume and/or increased arteriovenous oxygen difference at peak exercise and is typical of individuals with a high degree of cardiovascular fitness. Despite the airflow obstruction on resting pulmonary function tests,

Table 10.11.2

Selected Exercise Data

Measurement	Predicted	Measured	Predicted	Measured
Age		66		76
Peak $\dot{V}O_2$ (L/min)	1.98	2.50	1.64	2.12
Maximum heart rate (beats/min)	154	156	144	145
Maximum O_2 pulse (mL/beat)	12.8	16.4	11.4	16.3
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	9.6	10.3	9.1
AT (L/min)	>0.92	1.55	>0.78	1.37
Blood pressure (mm Hg [rest, peak exercise])		148/98, 186/86		118/82, 186/141
Maximum $\dot{V}E$ (L/min)		109		84
Exercise breathing reserve (L/min)	>15	19	>15	47
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.8	28.0	29.8	32.7

he had normal ventilatory parameters during exercise, including an adequate breathing reserve, and normal values for oxygen saturation and ventilatory equivalents. Repeat testing at age 76 (Tables 10.11.2 and 10.11.4 and Fig. 10.11.2) again demonstrated peak $\dot{V}O_2$ and anaerobic threshold above the average predicted values, and cardiorespiratory response patterns (Fig. 10.11.2) that were very similar to the earlier test. Table 10.11.5 shows results of seven exercise tests performed over 10 years showing a small but progressive age-related decline in peak heart rate and peak $\dot{V}O_2$.

Conclusion

This physically active individual with mild airway disease has maintained above-average exercise capacity while demonstrating normal age-related declines in cardiovascular function.

Table 10.11.3

Air Breathing, Age 66

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	148/98	63	11	6.3	0.17	0.24	3.9	0.70			102			36			37	26	
0.5	Rest		63	12	6.7	0.17	0.26	4.1	0.66			100			35			39	26	
1.0	Rest		62	11	6.9	0.18	0.26	4.2	0.69			101			35			39	27	
1.5	Rest		62	13	6.5	0.16	0.24	3.8	0.66			98			37			42	27	
2.0	Rest		66	11	8.7	0.25	0.36	5.5	0.69			97			37			35	24	
2.5	Rest		63	10	6.8	0.20	0.28	4.5	0.72			100			37			34	24	
3.0	Unloaded	148/98	72	15	15.2	0.43	0.54	7.5	0.80			105			35			35	28	
3.5	Unloaded		72	14	14.5	0.43	0.50	6.9	0.85			108			35			34	29	
4.0	Unloaded		69	14	13.8	0.40	0.47	6.8	0.85			108			36			34	29	
4.5	Unloaded		73	10	14.3	0.45	0.48	6.6	0.93			110			36			32	30	
5.0	Unloaded		72	10	10.1	0.30	0.37	5.2	0.80			104			38			33	27	
5.5	Unloaded		72	11	13.3	0.44	0.56	7.8	0.79			101			39			30	24	
6.0	10		74	12	14.0	0.43	0.46	6.3	0.92			109			36			33	30	
6.5	18		76	12	13.5	0.43	0.50	6.5	0.87			106			37			32	27	
7.0	29		80	10	12.3	0.39	0.51	6.4	0.77			100			39			31	24	
7.5	40		77	13	16.5	0.53	0.67	8.6	0.80			102			38			31	25	
8.0	46		85	11	17.9	0.62	0.79	9.3	0.79			99			39			29	23	
8.5	55		88	11	20.3	0.73	0.90	10.3	0.81			100			39			28	22	
9.0	70		89	12	22.3	0.80	0.98	11.0	0.81			99			40			28	23	
9.5	81		93	13	25.4	0.91	1.09	11.8	0.83			99			40			28	23	
10.0	87		95	15	28.9	1.03	1.23	12.9	0.84			101			39			28	24	
10.5	97		98	17	31.9	1.13	1.34	13.7	0.85			102			39			28	24	
11.0	107		105	19	36.6	1.30	1.47	14.0	0.89			104			39			28	25	
11.5	119		107	17	36.3	1.35	1.53	14.3	0.88			102			40			27	24	
12.0	126		114	18	43.5	1.58	1.67	14.7	0.94			105			39			28	26	
12.5	135		120	19	48.5	1.78	1.86	15.5	0.96			104			40			27	26	
13.0	156		126	21	56.4	1.97	1.95	15.5	1.01			108			39			29	29	
13.5	164		129	23	62.3	2.11	2.02	15.6	1.05			110			38			30	31	
14.0	183		133	24	62.9	2.15	2.05	15.4	1.05			110			38			29	31	
14.5	175		140	27	69.8	2.32	2.16	15.5	1.07			111			37			30	32	
15.0	189	186/86	141	30	76.4	2.48	2.24	15.9	1.11			113			36			31	34	
15.5	201		145	29	79.1	2.57	2.31	16.0	1.11			114			36			31	34	
16.0	217		148	31	85.7	2.73	2.38	16.1	1.14			115			35			31	36	
16.5	217		151	34	95.2	2.91	2.48	16.4	1.18			117			34			33	38	
17.0	226		156	39	104.0	3.07	2.50	16.0	1.23			119			32			34	42	
17.5	Recovery		151	41	109.0	3.09	2.35	15.5	1.32			121			32			35	46	
18.0	Recovery		134	34	91.9	2.42	1.52	11.4	1.59			126			30			38	60	
18.5	Recovery	162/76	121	24	61.0	1.66	1.05	8.7	1.58			125			31			37	58	
19.0	Recovery		112	23	50.7	1.34	0.87	7.8	1.54			126			30			38	58	

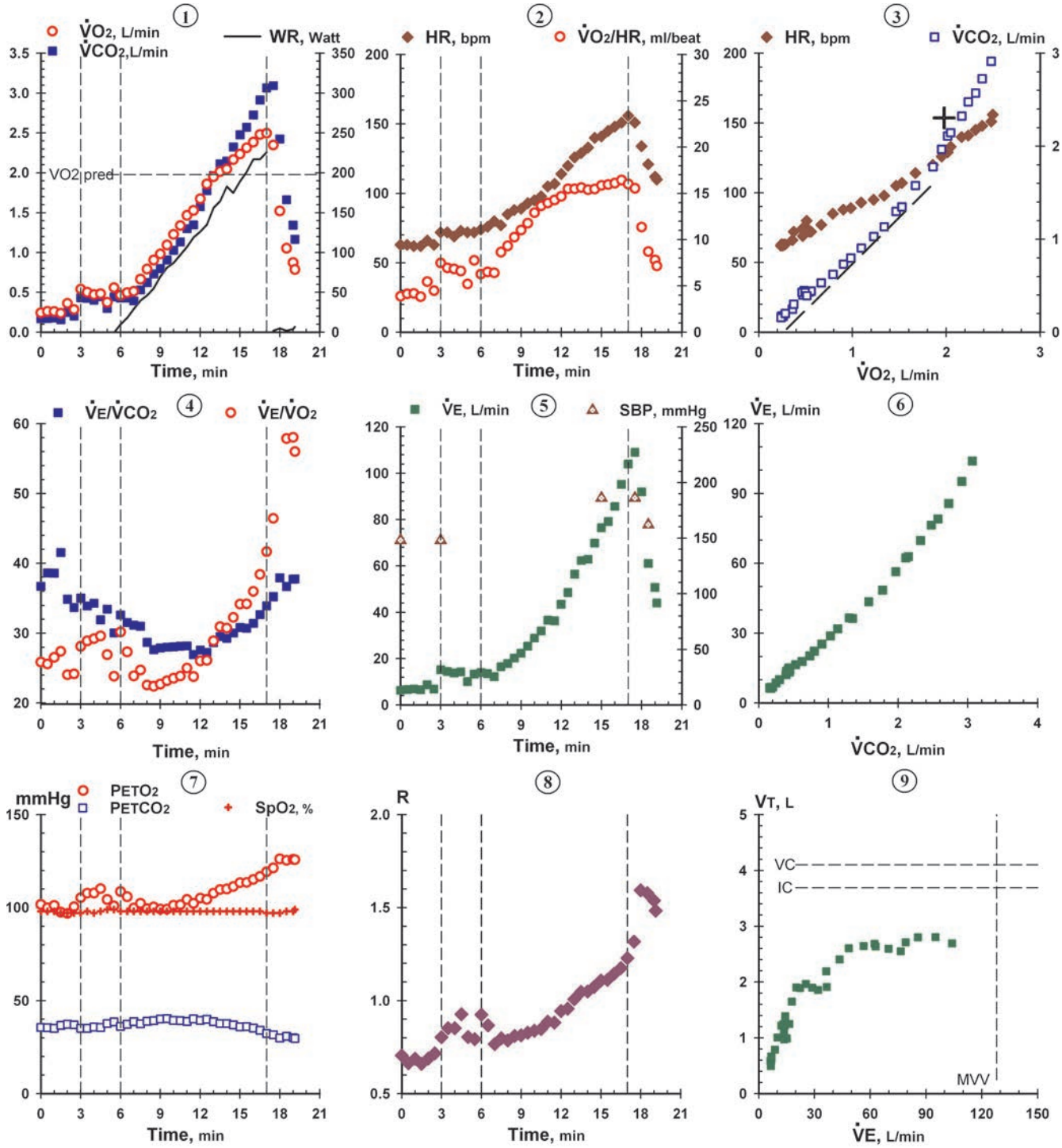

FIGURE 10.11.1. Age 66. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.11.4

Air Breathing, Age 76

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	118/82	70	15	11.7	0.25	0.31	4.5	0.80			114			27			46	37	
0.5	Rest		67	15	12.2	0.25	0.30	4.4	0.85			117			27			48	41	
1.0	Rest		74	13	12.0	0.26	0.29	3.9	0.90			117			27			46	42	
1.5	Rest		73	17	7.9	0.14	0.17	2.3	0.84			114			28			55	46	
2.0	Rest		77	17	10.5	0.22	0.29	3.8	0.76			111			29			48	36	
2.5	Rest		77	16	10.4	0.22	0.28	3.6	0.79			113			28			48	38	
3.0	Unloaded	129/93	79	12	13.5	0.33	0.41	5.2	0.81			112			29			41	33	
3.5	Unloaded		78	11	16.5	0.41	0.47	6.0	0.88			115			28			40	35	
4.0	Unloaded		79	10	17.5	0.43	0.45	5.7	0.96			118			28			40	39	
4.5	Unloaded		81	9	18.0	0.44	0.44	5.4	1.00			119			27			41	41	
5.0	Unloaded	138/94	81	12	15.2	0.37	0.39	4.8	0.95			118			28			42	39	
5.5	Unloaded		80	13	17.4	0.42	0.50	6.2	0.84			114			28			42	35	
6.0	7		78	13	15.4	0.37	0.44	5.6	0.85			114			29			42	35	
6.5	17		80	12	15.0	0.36	0.43	5.3	0.84			115			28			42	35	
7.0	26	134/99	78	13	19.4	0.49	0.57	7.3	0.85			114			29			40	34	
7.5	36		85	11	18.5	0.44	0.47	5.6	0.94			118			27			42	39	
8.0	47		78	13	18.2	0.48	0.60	7.7	0.79			111			30			38	30	
8.5	56		87	12	21.4	0.57	0.72	8.3	0.78			110			30			38	30	
9.0	66		94	12	23.7	0.64	0.79	8.4	0.80			111			30			37	30	
9.5	76		88	14	26.3	0.72	0.92	10.4	0.78			109			31			37	29	
10.0	86		92	14	25.5	0.72	0.91	9.9	0.79			107			33			36	28	
10.5	96	173/115	96	15	28.5	0.85	1.12	11.7	0.76			104			34			33	25	
11.0	106		104	16	33.7	0.99	1.19	11.4	0.83			109			33			34	28	
11.5	115		104	17	33.5	1.02	1.28	12.3	0.80			106			34			33	26	
12.0	126		114	16	37.6	1.15	1.37	12.0	0.84			107			34			33	27	
12.5	136	184/136	117	19	45.9	1.36	1.54	13.2	0.88			110			33			34	30	
13.0	146		116	19	45.9	1.38	1.54	13.3	0.89			110			34			33	30	
13.5	156		108	21	49.8	1.48	1.64	15.1	0.91			111			33			34	30	
14.0	165		126	21	54.8	1.62	1.74	13.8	0.93			111			34			34	31	
14.5	175		131	24	62.0	1.74	1.78	13.6	0.97			114			32			36	35	
15.0	185		120	28	67.0	1.86	1.91	15.9	0.97			115			32			36	35	
15.5	195	186/141	120	28	68.2	1.91	1.93	16.1	0.99			116			31			36	35	
16.0	205		125	30	74.7	2.05	2.04	16.3	1.01			116			31			36	37	
16.5	215		145	29	77.4	2.14	2.04	14.1	1.05			117			31			36	38	
17.0	225		130	32	83.6	2.27	2.12	16.3	1.07			118			31			37	39	
17.5	Recovery		123	30	73.5	1.99	1.76	14.3	1.13			119			31			37	42	
18.0	Recovery		114	24	54.0	1.38	1.06	9.3	1.29			123			29			39	51	
18.5	Recovery	162/76	107	18	37.3	0.97	0.75	7.0	1.30			123			30			38	50	
19.0	Recovery		101	16	27.6	0.72	0.59	5.8	1.23			121			30			38	47	
19.5	Recovery		94	15	26.0	0.68	0.57	6.1	1.19			121			30			38	45	
20.0	Recovery		94	17	23.8	0.62	0.56	5.9	1.12			119			31			38	43	

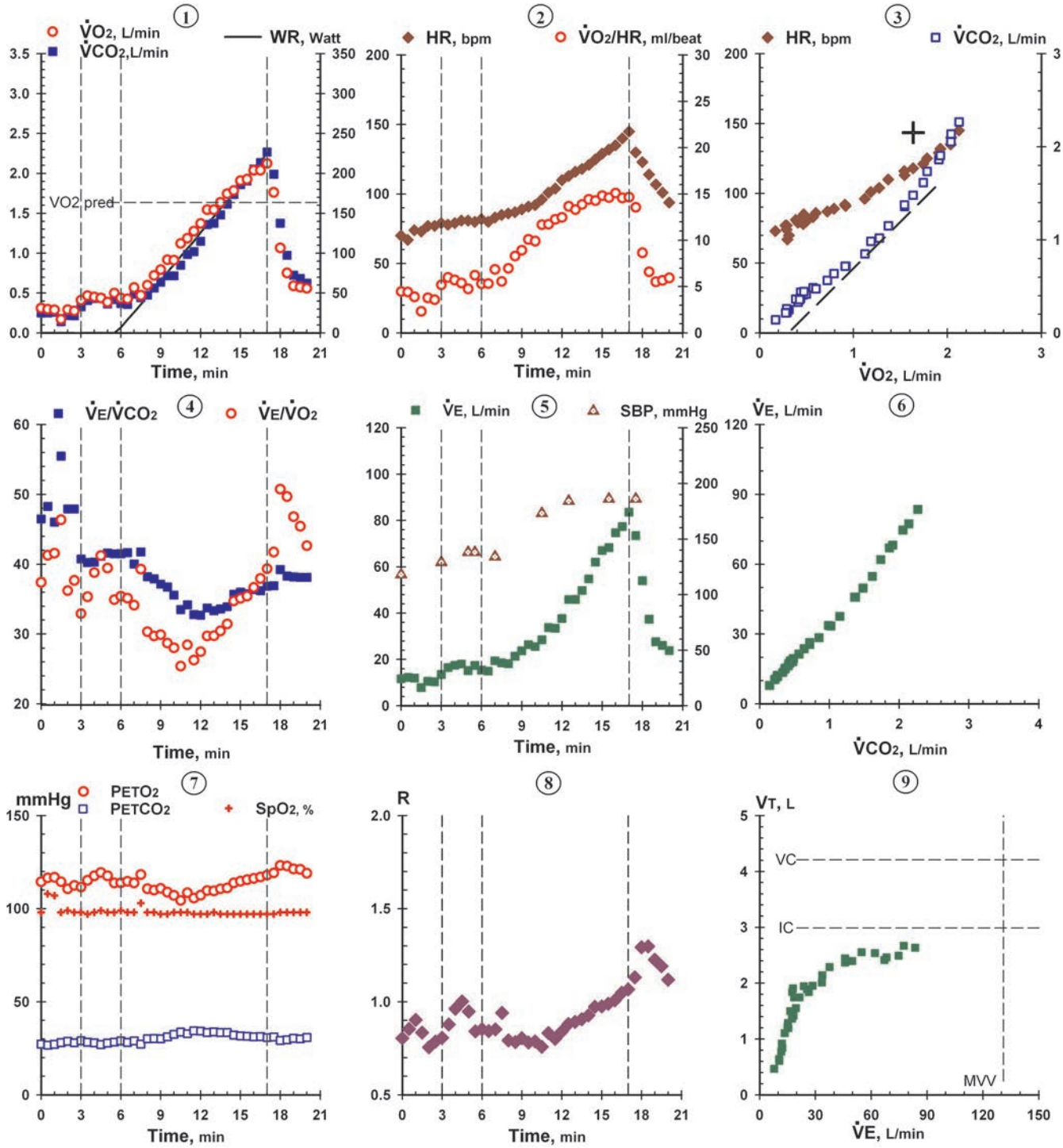

FIGURE 10.11.2. Age 76. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.11.5

Results of Serial Testing over 10 Years

Age (Years)	Peak $\dot{V}O_2$ (L/min)	*AT* (L/min)	Peak heart rate (beats/min)	Peak O_2 pulse (mL/beat)	$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest
66	2.50	1.55	155	16.1	28
68	2.49	1.70	158	15.8	29
70	2.30	1.68	156	14.7	30
71	2.36	1.80	150	15.7	30
73	2.29	1.70	151	15.2	30
74	2.31	1.55	144	16.0	29
76	2.12	1.37	148	14.3	33

Case 12 Chronic Heart Failure: Nonischemic Cardiomyopathy

CLINICAL FINDINGS

A 41-year-old man had been disabled from work as a brickworker, woodworker, sandblaster, and security guard due to a back injury 9 years prior to this study. Exercise testing was requested as part of an evaluation for asbestos-related disease. He reported a 3-year history of dyspnea and productive cough and had been given diagnoses of asthmatic bronchitis and "probable" pulmonary asbestosis. He was diagnosed with hypertension 6 years earlier. He denied smoking but had repeated hospitalizations for alcoholism. Current medications included propranolol, hydrochlorothiazide, theophylline, and potassium chloride. Auscultation of the heart and lungs were normal, as were chest radiographs and the resting ECG.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes, after which the work rate was increased 20 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. He stopped exercise with complaints of shortness of breath, lightheadedness, and leg fatigue. One premature ventricular contraction occurred during exercise, but ECGs were otherwise unchanged from rest.

Table 10.12.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		41
Sex		Male
Height (cm)		170
Weight (kg)	74	78
Hematocrit (%)		44
VC (L)	3.95	4.00
IC (L)	2.63	3.30
TLC (L)	5.58	5.28
FEV_1 (L)	3.16	3.43
FEV_1/VC (%)	80	86
MVV (L/min)	137	118
D_{LCO} (mL/mm Hg/min)	25.8	24.7

INTERPRETATION

Comments

Resting pulmonary function (Table 10.12.1) was normal.

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and anaerobic threshold were reduced (Tables 10.12.2 and 10.12.3), leading to the flowchart in Figure 8.4. The breathing reserve was normal (branch point 4.1), and the

Table 10.12.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.64	1.75
Maximum heart rate (beats/min)	179	150
Maximum O_2 pulse (mL/beat)	14.7	11.7
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.3
AT (L/min)	>1.11	0.85
Blood pressure (mm Hg [rest, max])		132/87, 204/108
Maximum $\dot{V}E$ (L/min)		78
Exercise breathing reserve (L/min)	>15	40
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.2	24.1
PaO_2 (mm Hg [rest, max ex])		87, 117
$P(A-a)O_2$ (mm Hg [rest, max ex])		4, 3
$PaCO_2$ (mm Hg [rest, max ex])		46, 39
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		2, –2
V_D/V_T (rest, heavy ex)		0.36, 0.23
HCO_3^- (mEq/L [rest, 2-min recov])		27, 18

ventilatory equivalent for CO_2 at the anaerobic threshold (branch point 4.3) and the indices of ventilation–perfusion matching were normal. These findings indicate that the patient does not have an abnormal pulmonary circulation but does have a nonpulmonary O_2 flow problem. The hematocrit was normal (branch point 4.4), so this was most likely due to cardiovascular disease. There were no ECG changes. His $\Delta\dot{V}O_2/\Delta WR$ was low, and he had a low but rising O_2 pulse at maximum work rate (panel 2, Fig. 10.12.1). The patient's blood pressure response to exercise and heart rate reserve were normal (Table 10.12.2), and he did not have leg pain with exercise, making peripheral arterial disease unlikely. Because beta-blocker therapy ordinarily results in a high O_2 pulse at peak exercise, the finding of a low O_2 pulse suggests a low stroke volume due to primary heart disease, since pulmonary vascular disease appears unlikely.

Conclusion

This patient had limitation to exercise at an abnormally low level due to cardiovascular dysfunction. A primary cardiac disorder was suspected because there were no specific findings to implicate pulmonary vascular, peripheral arterial, or coronary artery disease as the basis for the findings of impaired O_2 transport. Subsequent echocardiography confirmed the diagnosis of cardiomyopathy with left ventricular systolic dysfunction, perhaps due to alcoholism. There were no findings on this evaluation to support the prior suspicion of asbestosis.

Table 10.12.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	132/87								7.39	27		88			45				
0.5	Rest		73	19	7.4	0.16	0.21	2.9	0.76			98			43			36	28	
1.0	Rest		74	21	8.3	0.19	0.25	3.4	0.76			99			42			34	26	
1.5	Rest		72	20	6.7	0.15	0.20	2.8	0.75			97			43			33	25	
2.0	Rest	126/84	71	17	6.4	0.14	0.19	2.7	0.74	7.39	27	96	87	4	44	46	2	35	26	0.36
2.5	Rest		73	21	8.4	0.20	0.25	3.4	0.80			98			43			33	26	
3.0	Rest		73	20	7.4	0.17	0.22	3.0	0.77			99			43			34	26	
3.5	Unloaded		82	31	11.0	0.27	0.34	4.1	0.79			98			44			31	25	
4.0	Unloaded		86	34	12.5	0.35	0.45	5.2	0.78			95			44			27	21	
4.5	Unloaded		85	30	15.1	0.45	0.58	6.8	0.78			95			44			28	22	
5.0	Unloaded		84	19	12.9	0.41	0.55	6.5	0.75			93			46			28	21	
5.5	Unloaded		85	20	12.4	0.40	0.50	5.9	0.80			97			45			27	21	
6.0	Unloaded	138/84	85	21	13.8	0.45	0.54	6.4	0.83	7.37	27	99	88	8	45	47	2	27	22	0.27
6.5	20		87	21	14.6	0.49	0.58	6.7	0.84			99			45			26	22	
7.0	20		86	22	15.7	0.54	0.62	7.2	0.87			100			46			26	22	
7.5	40	147/90	92	23	17.0	0.59	0.69	7.5	0.86	7.38	28	95	94	4	48	48	2	26	22	0.26
8.0	40		97	25	20.3	0.72	0.79	8.1	0.91			101			46			25	23	
8.5	60		99	25	20.5	0.75	0.80	8.1	0.94			100			48			25	23	
9.0	60		105	25	23.6	0.90	0.89	8.5	1.01			103			47			24	24	
9.5	80		107	26	26.4	1.03	0.98	9.2	1.05			104			47			23	25	
10.0	80	159/90	115	27	31.2	1.20	1.05	9.1	1.14	7.36	26	107	103	5	48	47	–1	24	28	0.22
10.5	100		117	25	31.7	1.24	1.09	9.3	1.14			106			48			24	27	
11.0	100		121	25	38.3	1.45	1.18	9.8	1.23			109			48			25	31	
11.5	120		126	30	41.9	1.61	1.27	10.1	1.27			110			47			24	31	
12.0	120	192/105	129	31	46.2	1.71	1.30	10.1	1.32	7.35	24	112	111	3	46	44	–2	25	34	0.22
12.5	140		137	31	51.5	1.89	1.41	10.3	1.34			113			45			26	35	
13.0	140		144	32	57.0	2.06	1.50	10.4	1.37			115			44			26	36	
13.5	160		148	37	69.3	2.31	1.64	11.1	1.41			118			42			29	40	
14.0	160	204/108	150	40	77.6	2.48	1.75	11.7	1.42	7.34	21	118	117	3	41	39	–2	30	42	0.25
14.5	Recovery		144	37	61.0	1.90	1.36	9.4	1.40			118			41			30	43	
15.0	Recovery		129	34	45.8	1.43	1.02	7.9	1.40			115			43			30	42	
15.5	Recovery		127	30	37.0	1.13	0.81	6.4	1.40			113			45			30	43	
16.0	Recovery	150/78	124	36	30.1	0.87	0.66	5.3	1.32	7.28	18	116	116	3	41	38	–3	31	41	0.24

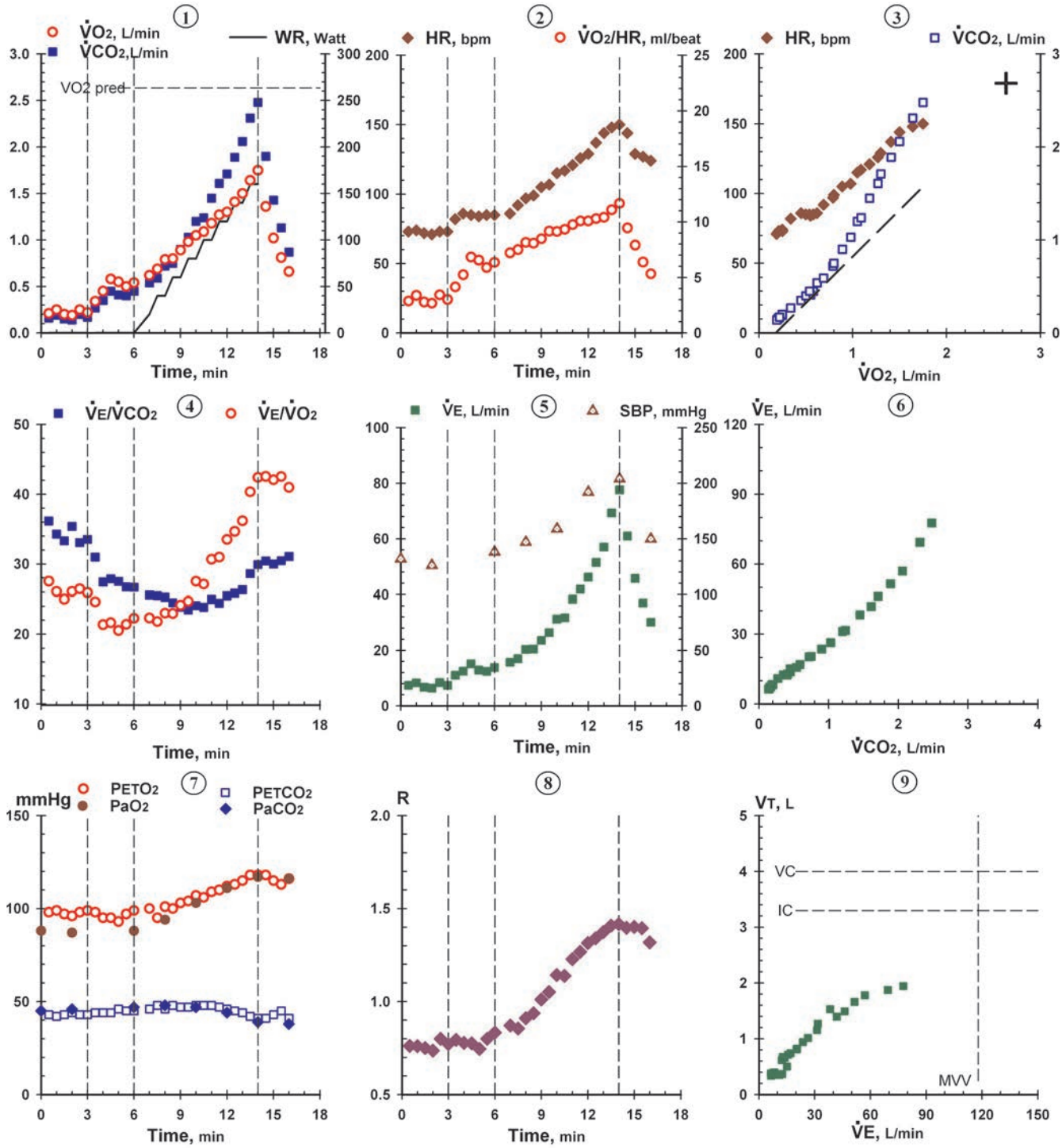

FIGURE 10.12.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 13 Chronic Heart Failure: Before and after Therapy

CLINICAL FINDINGS

A 64-year-old retired man was enrolled in a study of angiotensin-converting enzyme (ACE) inhibitor therapy for chronic systolic heart failure. He had episodic shortness of breath for 11 years and had been hospitalized repeatedly for congestive heart failure exacerbations without evidence of prior myocardial infarction or valvular heart disease. Medical history also included systemic hypertension and asthma. He was a former cigarette smoker. His medications included digoxin, furosemide, hydralazine, potassium chloride, prednisone, ranitidine, occasional inhaled albuterol, and diazepam. Examination revealed a heavy-set man without peripheral edema or abnormal physical findings on examination of the chest. Chest radiographs showed cardiomegaly and Kerley B lines; resting ECG showed left atrial enlargement and probable left ventricular hypertrophy. Exercise studies were performed after medical stabilization and every several weeks during 3 months of a drug study in which an ACE inhibitor was added to his therapy. The first and final exercise tests of this period are presented.

EXERCISE FINDINGS

On both tests, the patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased in a ramp pattern by 10 W per minute to tolerance. Blood pressure was measured with a sphygmomanometer. On both occasions, the patient was well motivated and cooperative and stopped exercise because of generalized fatigue. He had no chest pain, arrhythmia, or abnormal ST-T wave changes.

Table 10.13.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		64
Sex		Male
Height (cm)		170
Weight (kg)	73	82
VC (L)	3.65	2.70 (2.80[a])
IC (L)	2.43	1.92
TLC (L)	5.95	4.33
FEV_1 (L)	2.92	2.01 (2.30[a])
FEV_1/VC (%)	80	74
MVV (L/min)	117	80 (92[a])
DLCO (mL/mm Hg/min)	23.4	22
Hematocrit		44

[a]After 4 breaths of aerosolized albuterol.

INTERPRETATION

Comments

At the time of the first exercise test, resting pulmonary function studies showed ventilatory restriction and mild airway obstruction with some improvement with inhaled albuterol (Table 10.13.1).

Analysis

In the first study, referring to Flowchart 1 (Fig. 8.1), the patient had a reduced peak $\dot{V}O_2$ and anaerobic threshold (Tables 10.13.2 and 10.13.3 and Fig. 10.13.1). Referring to Flowchart 4 (Fig. 8.4), the breathing reserve was high (branch point 4.1), and the $\dot{V}E/\dot{V}CO_2$ at the anaerobic threshold was also high (branch point 4.3), suggesting an abnormal pulmonary circulation. Because the oxygenation

Table 10.13.2

Selected Exercise Data

Measurement	Predicted	First study	Final study
Peak $\dot{V}O_2$ (L/min)	2.03	0.91	1.34
Maximum heart rate (beats/min)	156	131	160
Maximum O_2 pulse (mL/beat)	13.0	7.0	9.0
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.0	9.2
AT (L/min)	>0.89	0.6	1.0
Blood pressure (mm Hg [rest, max])		112/95, 139/88	139/88, 204/104
Maximum $\dot{V}E$ (L/min)		44	55
Exercise breathing reserve (L/min)	>15	36	25
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.6	37.6	30.2

appeared normal (data not shown) (branch point 4.5), we consider moderate to severe left ventricular failure. The patient has other physiologic features of this condition, including low O_2 pulse and low $\Delta\dot{V}O_2/\Delta WR$. The reduced and slowly increasing O_2 pulse during exercise and the transient increase immediately after exercise stopped are most consistent with left ventricular dysfunction.

After 3 months of treatment with an ACE inhibitor, the maximum work rate, peak $\dot{V}O_2$, maximum O_2 pulse, anaerobic threshold, and $\Delta\dot{V}O_2/\Delta WR$ findings were considerably improved (Table 10.13.4 and Fig. 10.13.2).

Conclusion

This study is presented to show the findings of severe left ventricular dysfunction, as may be seen with cardiomyopathy of any cause, and the improvement in the functional abnormalities with effective therapy.

Table 10.13.3

First Study

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
0.5	Rest	112/95	105	19	17.4	0.42	0.42	4.0	1.00			114			36			38	38	
1.0	Rest		101	20	13.2	0.29	0.34	3.4	0.85			105			40			40	34	
1.5	Rest		101	21	16.6	0.38	0.40	4.0	0.95			111			37			39	37	
2.0	Rest		104	19	13.7	0.28	0.31	3.0	0.90			110			38			43	39	
2.5	Rest		105	24	17.2	0.37	0.41	3.9	0.90			110			37			41	37	
3.0	Rest		105	22	15.6	0.33	0.34	3.2	0.97			114			36			42	40	
3.5	Unloaded		107	28	19.9	0.41	0.43	4.0	0.95			113			36			43	41	
4.0	Unloaded		108	29	19.4	0.39	0.41	3.8	0.95			113			36			43	41	
4.5	Unloaded		109	26	16.9	0.32	0.35	3.2	0.91			112			37			46	42	
5.0	Unloaded		110	26	21.5	0.46	0.47	4.3	0.98			113			35			42	41	
5.5	Unloaded		106	27	16.6	0.32	0.35	3.3	0.91			110			38			45	41	
6.0	Unloaded		111	28	21.4	0.45	0.46	4.1	0.98			114			35			42	41	
6.5	3		112	29	19.7	0.45	0.53	4.7	0.85			104			40			38	33	
7.0	8		115	24	20.0	0.45	0.46	4.0	0.98			114			35			40	39	
7.5	13		117	28	21.1	0.45	0.48	4.1	0.94			112			36			42	39	
8.0	18		117	25	21.2	0.49	0.53	4.5	0.92			111			37			39	36	
8.5	23		118	26	22.5	0.51	0.53	4.5	0.96			113			36			40	38	
9.0	28		118	25	22.8	0.54	0.57	4.8	0.95			111			37			38	36	
9.5	33		120	27	26.8	0.53	0.60	5.0	0.88			116			35			46	41	
10.0	38		121	26	28.4	0.68	0.65	5.4	1.05			117			35			39	40	
10.5	43		124	29	28.4	0.73	0.67	5.4	1.09			116			37			36	39	
11.0	48		127	29	36.2	0.87	0.73	5.7	1.19			121			32			39	46	
11.5	53		130	31	38.2	0.92	0.76	5.8	1.21			122			33			39	47	
12.0	58	139/88	131	33	43.5	1.09	0.89	6.8	1.22			121			33			37	46	
12.5	Recovery		130	22	32.1	1.00	0.91	7.0	1.10			112			40			30	33	
13.0	Recovery		125	24	34.0	0.91	0.70	5.6	1.30			121			35			35	46	
13.5	Recovery		123	23	29.0	0.81	0.62	5.0	1.31			120			37			33	44	
14.0	Recovery		123	22	24.8	0.64	0.46	3.7	1.39			123			35			36	50	

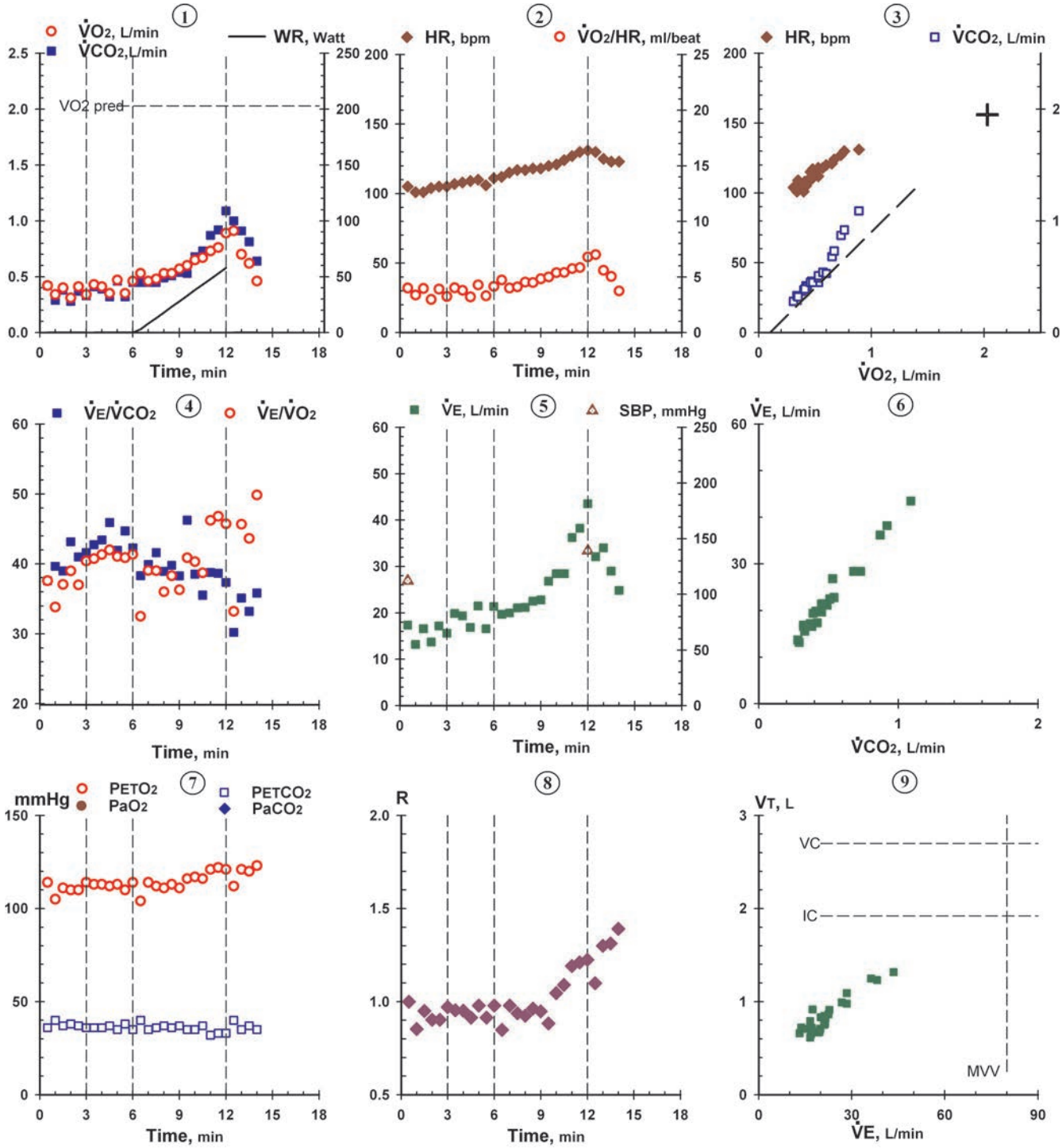

FIGURE 10.13.1. First study. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

TABLE 10.13.4

Final Study

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	139/88	92	17	14.0	0.34	0.40	4.3	0.85			104			41			37	31	
1.0	Rest		87	16	12.0	0.30	0.35	4.0	0.86			103			42			35	30	
1.5	Rest		92	15	11.0	0.28	0.33	3.6	0.85			103			42			35	29	
2.0	Rest		90	19	11.0	0.19	0.24	2.7	0.79			104			42			49	39	
2.5	Rest		95	17	12.0	0.29	0.35	3.7	0.83			104			42			36	30	
3.0	Rest		91	19	13.0	0.29	0.32	3.5	0.91			106			41			39	36	
3.5	Unloaded		95	19	16.0	0.43	0.54	5.7	0.80			98			43			33	27	
4.0	Unloaded		98	20	14.0	0.35	0.43	4.4	0.81			101			43			35	29	
4.5	Unloaded		100	22	18.0	0.48	0.54	5.4	0.89			104			41			34	30	
5.0	Unloaded		99	21	18.0	0.48	0.58	5.9	0.83			100			43			34	28	
5.5	Unloaded		102	21	18.0	0.48	0.54	5.3	0.89			104			42			34	30	
6.0	Unloaded		103	22	17.0	0.43	0.50	4.9	0.86			103			42			35	30	
6.5	3		105	21	16.0	0.41	0.49	4.7	0.84			102			43			35	29	
7.0	8		106	20	18.0	0.49	0.59	5.6	0.83			102			42			33	28	
7.5	13		106	20	20.0	0.56	0.67	6.3	0.84			101			42			33	27	
8.0	18		108	23	20.0	0.56	0.68	6.3	0.82			101			42			32	27	
8.5	23		110	24	22.0	0.61	0.76	6.9	0.80			100			42			33	26	
9.0	28		110	23	22.0	0.60	0.73	6.6	0.82			101			44			33	27	
9.5	33		111	22	19.0	0.54	0.69	6.2	0.78			96			44			32	25	
10.0	38		113	22	23.0	0.74	0.94	8.3	0.79			95			44			29	22	
10.5	43		117	24	24.0	0.73	0.83	7.1	0.88			102			43			30	26	
11.0	48		122	24	28.0	0.86	0.94	7.7	0.91			104			42			30	28	
11.5	53		127	23	28.0	0.86	0.93	7.3	0.92			106			41			30	28	
12.0	58		134	23	30.0	0.96	1.05	7.8	0.91			105			42			29	27	
12.5	63		138	25	36.0	1.09	1.08	7.8	1.01			111			40			31	31	
13.0	68		143	25	38.0	1.19	1.13	7.9	1.05			111			40			30	32	
13.5	73		143	25	41.0	1.26	1.13	7.9	1.12			113			40			31	34	
14.0	78		152	30	51.0	1.46	1.22	8.0	1.20			118			36			33	40	
14.5	83		155	31	55.0	1.50	1.22	7.9	1.23			120			35			35	43	
15.0	88	204/104	160	29	52.0	1.44	1.14	7.1	1.26			120			36			34	43	
15.5	Recovery		148	25	46.0	1.56	1.34	9.1	1.16			111			43			28	33	
16.0	Recovery		128	24	41.0	1.36	0.98	7.7	1.39			117			41			29	40	
16.5	Recovery		130	23	36.0	1.16	0.78	6.0	1.49			119			41			29	44	
17.0	Recovery		123	21	29.0	0.91	0.61	5.0	1.49			119			41			30	45	

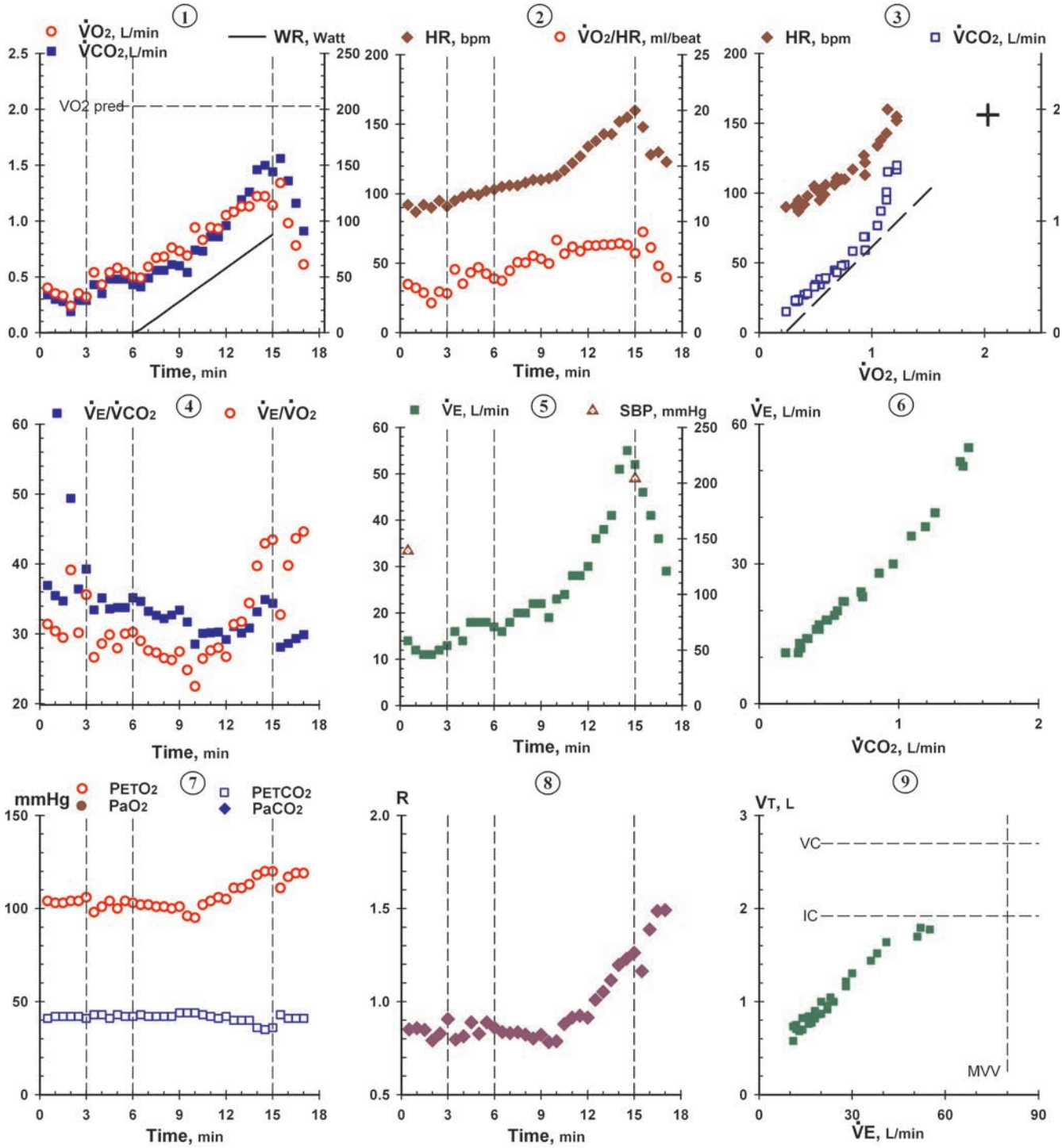

FIGURE 10.13.2. Final study. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 14 Chronic Heart Failure: Oscillatory Ventilation and Gas Exchange

CLINICAL FINDINGS

A 57-year-old homemaker without prior medical history presented with complaints of 6 months of shortness of breath, exercise limitation, and easy fatigability. She had two-pillow orthopnea and paroxysmal nocturnal dyspnea. She did not experience exertional chest pain. An echocardiogram reported a dilated cardiomyopathy with a 15% left ventricular ejection fraction. She was treated with lisinopril, digoxin, warfarin, atorvastatin, and furosemide, and referred for exercise testing to quantify the severity of her heart failure. At the time of referral, she was symptomatically improved on therapy and had clear breath sounds and only trace pretibial edema. Chest radiographs were normal except for mild left ventricular enlargement. Resting ECG revealed sinus rhythm and left bundle branch block with rare premature ventricular contractions.

EXERCISE FINDINGS

The patient was studied during exercise on a cycle ergometer (Fig. 10.14.1). After 3 minutes of rest, she pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased in a ramp pattern by 10 W per minute to her symptom-limited maximum. Blood pressure was measured with a sphygmomanometer. Arterial oxyhemoglobin saturation was estimated by pulse oximeter. The patient stopped exercise on her own volition because of leg fatigue. During unloaded cycling, premature ventricular contractions occurred at about one per minute, but these resolved at higher work rates. The ST segments did not change with exercise. At rest and during early exercise, an oscillatory breathing pattern with a period of about 1 minute was observed (Fig. 10.14.2).

INTERPRETATION

Comments

This patient has an idiopathic cardiomyopathy and symptoms compatible with New York Heart Association class II to III. Respiratory function showed mild airway obstruction and mild reduction in diffusing capacity (Table 10.14.1). A distinctly oscillatory pattern of $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ is seen at rest and at exercise intensities below the anaerobic threshold, as found in a subset of patients with left ventricular failure (Fig. 10.14.2).

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and anaerobic threshold are reduced (Tables 10.14.2 and 10.14.3). Referring to Flowchart 4 (Fig. 8.4), the breathing reserve is normal (branch point 4.1), whereas the ventilatory equivalent for CO_2 at the *AT* is high (branch point 4.3), implying an increased V_D/V_T.[1] This leads to the diagnostic category *abnormal pulmonary circulation* (branch point 4.5). To help distinguish between high $\dot{V}_A/\dot{Q}$ mismatch due to primary pulmonary vascular disease (left branch) and high $\dot{V}_A/\dot{Q}$ mismatch due to relative stasis of pulmonary blood flow caused by left ventricular failure (right branch), consider the arterial saturation (branch point 4.5). The normal arterial oxyhemoglobin saturation throughout exercise is more characteristic of the slow pulmonary blood flow (long transit time) of left ventricular dysfunction (right branch) as opposed to the shortened transit time associated with exercise arterial hypoxemia of primary pulmonary vascular disease (left branch).

The data in the nine-panel plots are graphed as 30-second averages, which is insufficient time resolution to fully appreciate the temporal pattern of change in $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$. When these variables are plotted using a moving average, a systematic oscillatory pattern is evident at rest and at low levels of exercise. This finding is seen in some patients with left ventricular failure and has features similar to Cheyne-Stokes respiration. The periodic (oscillatory) gas exchange pattern is analyzed in greater detail in Figure 10.14.2. The oscillations have a period of 1 minute from peak to peak and are greatest at rest and during mild-to-moderate exercise. The rise in $\dot{V}O_2$ begins first, followed by $\dot{V}CO_2$, $\dot{V}E$, and finally R.

We postulate that the oscillation in gas exchange is caused by oscillating pulmonary blood flow due to cyclic changes in systemic blood pressure in the presence of a heart that is functioning on the flat or descending limb of the Frank–Starling curve. The cyclic changes in arterial pressure are known as *Traube–Hering waves* and have a period of 0.75 to 1.5 minutes. These changes in arterial tone do not affect cardiac output (and therefore pulmonary blood flow) in normal individuals because cardiac output normally depends on venous return (ascending limb of the Frank–Starling curve). With left ventricular failure, however, the cardiac output is less dependent on cardiac preload (Starling's law of the heart) and more critically dependent on afterload. Thus, cardiac output and $\dot{V}O_2$ in patients with heart failure may vary with oscillations in vasomotor tone in the systemic arterial bed. $\dot{V}E$ may oscillate secondary to the pulmonary blood flow

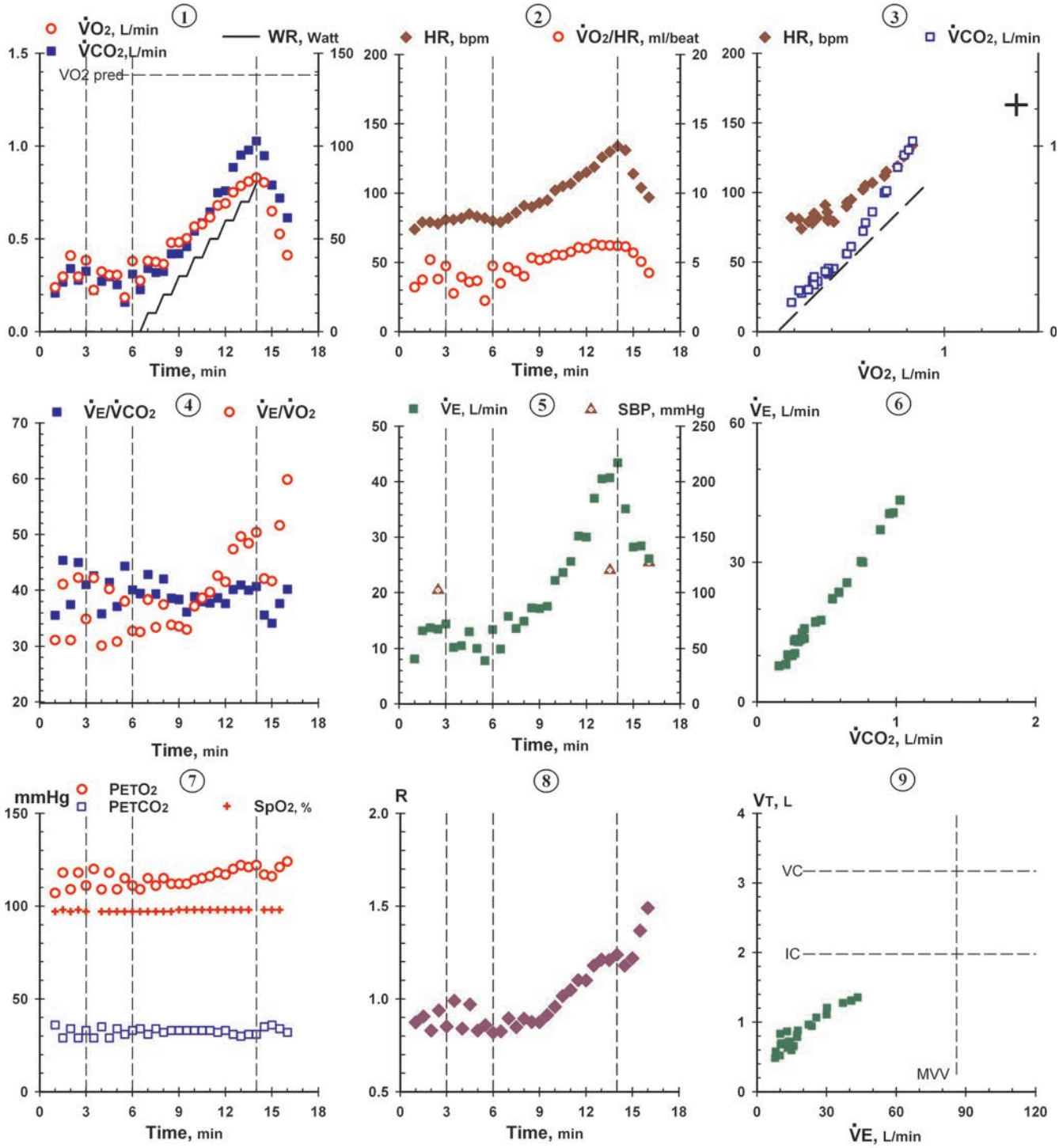

FIGURE 10.14.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

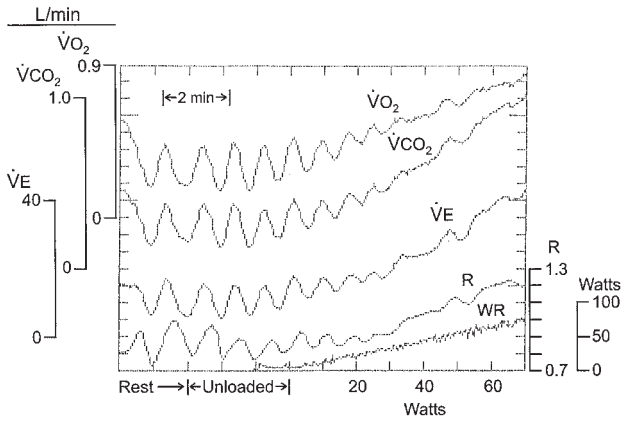

FIGURE 10.14.2. $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, R, and work rate (WR), from top to bottom, during rest and incremental exercise. Oscillations in the data have a period of 1 minute from peak to peak and are most prominent at rest and during moderate exercise. The inter-breath noise is reduced in this display by use of a moving interval (MI) average type of filtering. The breath-by-breath data were first converted into time-based data of 0.1 sec time intervals by interpolation. For each data point, the data in the MI window were fitted by a fifth-order polynomial, and the center point of the MI is given by the center point of the polynomial. This provides superior fitting of data with rapid changes in slope. Analysis of the sinusoid-like patterns showed that the peak-to-peak interval for oscillations of $\dot{V}O_2$ was 1 minute. The time delay following a $\dot{V}O_2$ peak to the peak of the other measured variables was 0.05 minute for $\dot{V}CO_2$, 0.1 minute for $\dot{V}E$, and 0.34 minute for R. These times are compatible with a primary oscillation of pulmonary blood flow followed by secondary changes in ventilation. See the Interpretation section for further discussion.

Table 10.14.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		57
Sex		Female
Height (cm)		168
Weight (kg)		59.1
Hematocrit (%)		38.5
VC (L)	3.27	3.17
IC (L)	2.18	1.98
ERV (L)	1.09	1.19
FEV_1 (L)	2.64	2.17
FEV_1/VC (%)	81	69
MVV (L/min)	97	86
D_{LCO} (mL/mm Hg/min)	22.7	17.8

Table 10.14.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.35	0.83
Maximum heart rate (beats/min)	163	134
Maximum O_2 pulse (mL/beat)	8.3	6.2
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	6.9
AT (L/min)	>0.70	0.53
Blood pressure (mm Hg [rest, max])		102/66, 120/85
Maximum $\dot{V}E$ (L/min)		43
Exercise breathing reserve (L/min)	>15	43
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.9	38.2
P_{ETCO_2} at *AT*	>40	33
$\dot{V}E$ vs. $\dot{V}CO_2$	<32	38
Sa_{O_2} (pulse oximeter, % [rest, exercise])	>95	98, 98

oscillation if arterial Pa_{CO_2}, Pa_{O_2}, and H^+ oscillate as a result of cyclic changes in pulmonary blood flow–alveolar ventilation mismatch. It is thought that the increased production of catecholamines during heavy exercise obliterates the changing vasomotor tone stimulus from the central nervous system.

An oscillatory gas exchange pattern is characteristic of some patients with more severe forms of left ventricular failure[2] and is an independent predictor of mortality in this population.

Conclusion

This patient is presented to illustrate the oscillatory pattern in $\dot{V}O_2$ and other abnormalities that are common findings during exercise among patients with left ventricular failure.

REFERENCES

1. Wasserman K, Zhang Y-Y, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. *Circulation*. 1997;96:2221–2227.
2. Ben-Dov I, Sietsema KE, Casaburi R, et al. Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. *Am Rev Respir Dis*. 1992;145:776–781.

Table 10.14.3

Air breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest		74	14	8.1	0.21	0.24	3.2	0.87			107			36			36	31	
1.0	Rest		79	21	13.2	0.27	0.30	3.7	0.91			118			29			45	41	
1.5	Rest		79	19	13.7	0.34	0.41	5.2	0.83			109			34			38	31	
2.0	Rest	102/66	78	20	13.5	0.28	0.30	3.8	0.94			118			29			45	42	
2.5	Rest		81	20	14.4	0.33	0.38	4.7	0.85			111			33			41	35	
3.0	Rest		81	15	10.2	0.22	0.22	2.8	0.99			120			29			43	42	
3.5	Unloaded		82	15	10.5	0.27	0.32	4.0	0.84			109			35			36	30	
4.0	Unloaded		85	15	13.0	0.30	0.31	3.6	0.97			118			29			41	40	
4.5	Unloaded		83	12	10.0	0.25	0.31	3.7	0.83			109			34			37	31	
5.0	Unloaded		82	16	7.8	0.16	0.18	2.2	0.86			115			31			44	38	
5.5	Unloaded		80	19	13.4	0.31	0.38	4.8	0.82			111			33			40	33	
6.0	Unloaded		79	19	9.9	0.23	0.28	3.5	0.83			109			34			39	33	
6.5	5		82	24	15.8	0.34	0.38	4.6	0.90			115			31			43	38	
7.0	10		86	21	13.6	0.32	0.38	4.4	0.85			111			34			39	33	
7.5	15		91	25	14.9	0.33	0.36	4.0	0.89			115			32			42	38	
8.0	20		90	22	17.3	0.42	0.48	5.3	0.88			112			33			39	34	
8.5	25		93	21	17.2	0.42	0.48	5.2	0.88			112			33			38	34	
9.0	30		95	20	17.6	0.46	0.50	5.3	0.91			112			33			36	33	
9.5	35		102	23	22.2	0.54	0.57	5.5	0.96			114			33			39	37	
10.0	40		105	25	23.6	0.59	0.58	5.5	1.02			115			33			38	39	
10.5	45		107	24	25.6	0.65	0.62	5.8	1.05			116			33			38	40	
11.0	50		112	25	30.2	0.75	0.68	6.1	1.10			118			32			39	43	
11.5	55		115	27	30.0	0.76	0.69	6.0	1.10			117			33			38	41	
12.0	60		119	29	37.0	0.89	0.75	6.3	1.18			120			31			40	47	
12.5	65		126	31	40.5	0.95	0.79	6.2	1.21			122			30			41	50	
13.0	70	120/85	130	31	40.7	0.98	0.81	6.2	1.21			121			31			40	48	
13.5	75		134	32	43.4	1.03	0.83	6.2	1.24			122			31			41	50	
14.0	Recovery		131	26	35.1	0.95	0.80	6.1	1.18			117			35			36	42	
14.5	Recovery		114	24	28.2	0.79	0.65	5.7	1.22			116			36			34	42	
15.0	Recovery		104	25	28.4	0.72	0.53	5.1	1.37			121			34			38	52	
15.5	Recovery	127/75	97	29	26.1	0.61	0.41	4.2	1.49			124			32			40	60	

Case 15 Chronic Heart Failure: Cardiomyopathy with Intraventricular Conduction Delay

CLINICAL FINDINGS

A 71-year-old man was enrolled in a clinical trial investigating treatment of chronic left ventricular systolic heart failure. At the time of testing, his medical therapies had been optimized with treatment that included diuretics, an angiotensin-converting enzyme (ACE) inhibitor, and beta-adrenergic blocker. He was tested while in a well-compensated state without findings of overt volume overload. Resting ECG showed a sinus rhythm and intraventricular conduction delay.

EXERCISE FINDINGS

The patient exercised on a cycle ergometer beginning with 2 minutes of unloaded pedaling at 60 rpm followed by continuous increase in the work rate by 10 W per minute until he stopped with symptoms of leg fatigue and shortness of breath. Blood pressure was measured intermittently by sphygmomanometer. There was no significant change in the ECG with exercise.

INTERPRETATION

Comment

Resting spirometry showed mildly reduced volumes without evidence of airflow obstruction (Table 10.15.1).

Table 10.15.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		71
Sex		Male
Height (cm)		175
Weight (kg)		94
VC (L)	3.67	3.09
IC (L)	2.43	2.38
FEV_1 (L)	2.83	2.42
FEV_1/VC (%)	77	78
MVV (L/min)	110	98

Table 10.15.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.97	1.03
Maximum heart rate (beats/min)	149	83
Maximum O_2 pulse (mL/beat)	13.2	13.5
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	5.7
AT (L/min)	>0.93	0.75
Blood pressure (mm Hg [rest, max])		100/60, 160/70
Maximum $\dot{V}E$ (L/min)		59
Exercise breathing reserve (L/min)	>15	39
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	29.2	44.5

Analysis

Peak $\dot{V}O_2$ and anaerobic threshold were both low (Tables 10.15.2 and 10.15.3 and Fig. 10.15.1), which leads from Flowchart 1 (Fig. 8.1) to Flowchart 4 (Fig. 8.4). The breathing reserve was normal (branch point 4.1), while the ventilatory equivalent for CO_2 at the *AT* was high (branch point 4.3). The normal pulse oximetry and the other confirmatory data within the box are consistent with moderate-to-severe LV failure. The $\Delta\dot{V}O_2/\Delta WR$ was lower than normal; in fact, $\dot{V}O_2$ appears to have leveled off without further increase over the final 90 seconds of exercise despite increasing work rate. The peak heart rate was also low, which is likely due at least in part to the beta-adrenergic blocker. The O_2 pulse increased over the first 2 minutes of the incremental work period, then reached a stable level that failed to increase with further increase in work rate. Although at end exercise the O_2 pulse was close to the predicted maximum value, with such a severely limited heart rate, failure to exceed the predicted O_2 pulse value implies a limited stroke volume response. In the early recovery period, there was a transient increase in O_2 pulse reflecting the delay in decrease in $\dot{V}O_2$ as heart rate began to decline. This suggests augmented stroke volume associated with the cessation of exercise. The ventilatory equivalents failed to decrease into the normal range, with the value for $\dot{V}E/\dot{V}CO_2$ at the anaerobic threshold being at

Table 10.15.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	100/60	63	19	15.2	0.28	0.30	4.7	0.94			118			26			54	51	
1.0	Rest		64	18	14.3	0.26	0.26	4.1	0.98			119			26			56	54	
1.5	Rest		64	18	12.9	0.23	0.25	3.8	0.95			119			27			55	52	
2.0	Rest		64	19	14.8	0.26	0.26	4.1	0.97			120			25			58	56	
2.5	Rest		64	18	14.5	0.25	0.25	3.9	1.00			121			25			58	59	
3.0	Rest		63	19	13.7	0.24	0.25	4.0	0.96			120			26			57	55	
3.5	Unloaded	120/60	69	26	15.1	0.27	0.35	5.0	0.77			111			29			56	43	
4.0	Unloaded		73	29	26.1	0.48	0.52	7.1	0.92			118			26			54	50	
4.5	Unloaded		73	27	21.3	0.46	0.58	8.0	0.79			109			31			46	37	
5.0	Unloaded		76	29	28.2	0.60	0.68	8.9	0.88			114			28			47	42	
5.5	5		78	31	31.5	0.68	0.75	9.6	0.90			114			29			47	42	
6.0	10		77	32	33.9	0.76	0.79	10.3	0.95			114			29			45	43	
6.5	15		75	31	36.9	0.82	0.81	10.8	1.01			116			29			45	46	
7.0	20	122/68	73	31	39.1	0.88	0.85	11.6	1.04			116			29			45	46	
7.5	25		71	31	41.6	0.95	0.89	12.6	1.06			117			29			44	47	
8.0	30	130/64	75	31	45.8	1.03	0.93	12.3	1.11			118			29			45	49	
8.5	35		75	35	51.3	1.10	0.93	12.3	1.18			121			27			47	55	
9.0	40		78	33	50.3	1.12	0.97	12.4	1.16			120			28			45	52	
9.5	45	140/72	83	38	58.5	1.24	1.02	12.3	1.22			122			26			47	58	
10.0	50		83	38	57.2	1.22	1.02	12.3	1.19			122			27			47	56	
10.5	55	160/70	81	40	58.8	1.23	1.03	12.7	1.19			122			26			48	57	
11.0	Recovery	160/70	76	37	56.8	1.20	1.03	13.5	1.17			122			26			47	55	
11.5	Recovery		77	35	52.4	1.13	0.98	12.7	1.15			122			27			46	54	
12.0	Recovery		74	33	44.0	0.93	0.73	9.9	1.27			123			27			47	60	
12.5	Recovery		69	32	39.3	0.79	0.57	8.2	1.39			125			26			50	69	
13.0	Recovery	138/66	72	25	28.5	0.58	0.42	5.8	1.38			125			27			50	68	
13.5	Recovery		70	26	23.2	0.46	0.36	5.2	1.28			125			26			50	64	

around 44. The high ventilatory equivalent is associated with elevated VD/VT. While not unique to the condition of heart failure, this is characteristic of moderate and severe heart failure and is one of a number of variables identified as markers of poor prognosis in that population.

Conclusion

This test demonstrates common exercise findings for a patient with left ventricular systolic dysfunction. Impaired heart rate responsiveness—either due to heart failure, medication, or both—probably contributes to exercise limitation.

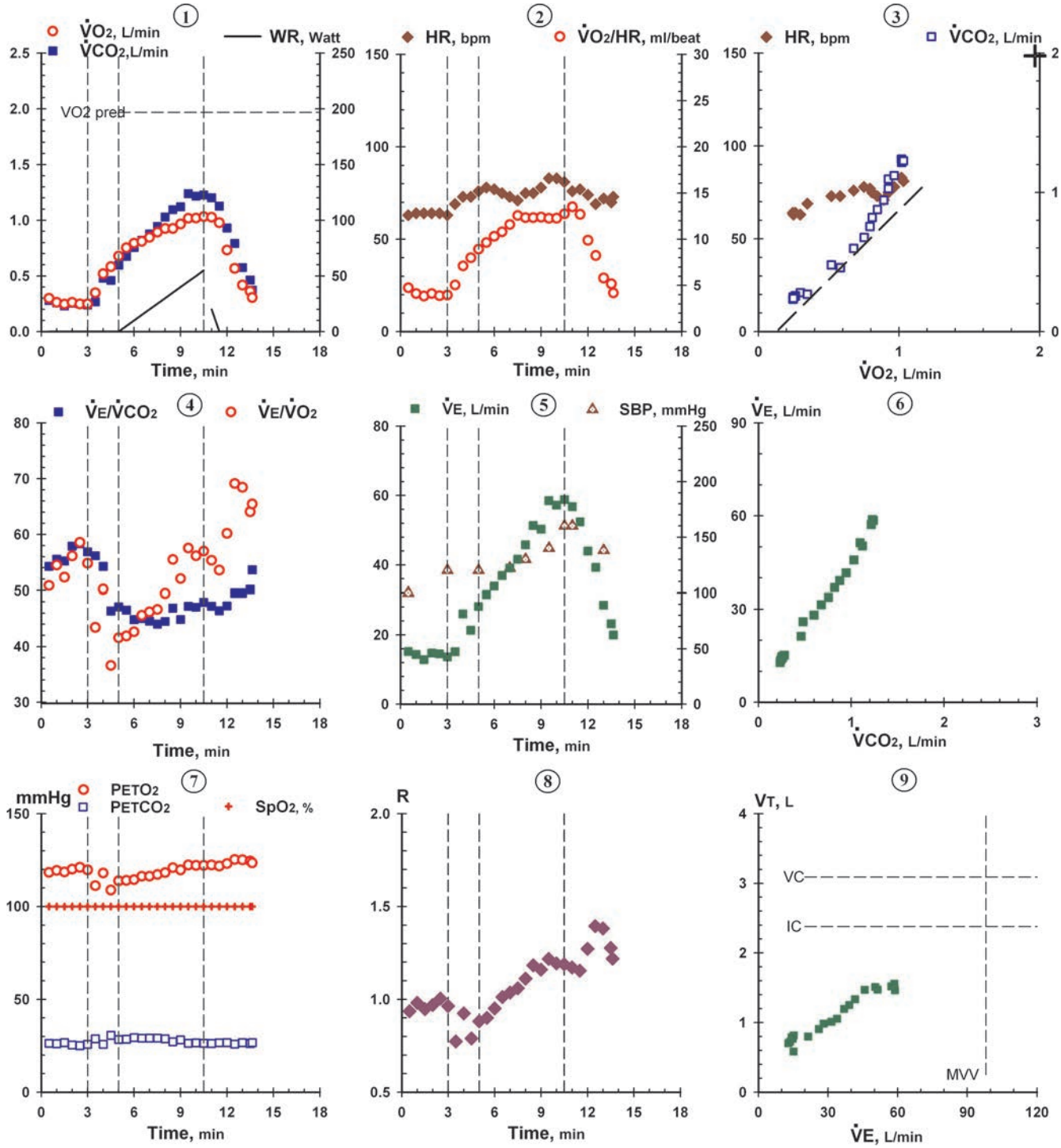

FIGURE 10.15.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 16 Myocardial Ischemia: Undiagnosed Angina and Hypertension

CLINICAL FINDINGS

A 58-year-old man was referred for exercise testing as part of a disability evaluation related to occupational exposure to asbestos and sandblasting. On review of systems, he reported episodic chest pain, originating in the mid-back and radiating around the left chest into the substernal area. The pain was brought on when walking on cold days and relieved in a few minutes by rest and had not previously been diagnosed or treated. He denied shortness of breath. A physical examination revealed no evidence of peripheral vascular disease, heart murmurs, or abnormal heart sounds. The resting 12-lead ECG was within normal limits.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 20 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of interscapular pain and right anterior chest pain. The ECG showed 2-mm ST-segment depressions in leads II, III, aVF, and V_3 through V_6 during exercise but returned to normal after 9 minutes of recovery. The chest pain resolved within 1 minute of cessation of exercise.

Table 10.16.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		58
Sex		Male
Height (cm)		173
Weight (kg)	76	82
Hematocrit (%)		41
VC (L)	4.09	4.04
IC (L)	2.73	3.39
TLC (L)	6.20	5.93
FEV_1 (L)	3.21	3.43
FEV_1/VC (%)	79	85
MVV (L/min)	135	155
DLCO (mL/mm Hg/min)	25.5	25.9

INTERPRETATION

Comments

Resting respiratory function was normal (Table 10.16.1).

Analysis

In Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ was reduced, whereas the anaerobic threshold was normal (Tables 10.16.2 and 10.16.3 and Fig. 10.16.1), which directs us through branch points 1.1, 1.2, and 1.3 to Flowchart 3 (Fig. 8.3). The breathing reserve (branch point 3.1) was high and the ECG

Table 10.16.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.25	1.47
Maximum heart rate (beats/min)	162	146
Maximum O_2 pulse (mL/beat)	13.9	10.3
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	7.2
AT (L/min)	>0.99	1.0
Blood pressure (mm Hg [rest, max])		174/81, 222/99
Maximum $\dot{V}E$(L/min)		75
Exercise breathing reserve (L/min)	>15	80
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.9	28.3
PaO_2 (mm Hg [rest, max ex])		87, 115
$P(A-a)O_2$ (mm Hg [rest, max ex])		18, 10
$PaCO_2$ (mm Hg [rest, max ex])		35, 29
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		−3, −6
VD/VT (rest, heavy ex)		0.21, 0.12
HCO^-_3 (mEq/L [rest, 2-min recov])		22, 16

Table 10.16.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest									7.42	22		91			35				
0.5	Rest		80	9	10.0	0.28	0.30	3.8	0.93			110			36			33	31	
1.0	Rest		74	11	9.5	0.25	0.29	3.9	0.86			109			35			34	30	
1.5	Rest		74	17	7.1	0.17	0.21	2.8	0.81			103			38			33	27	
2.0	Rest		77	10	9.5	0.27	0.37	4.8	0.73	7.41	22	98	87	18	38	35	–3	32	23	0.21
2.5	Rest		89	19	11.3	0.32	0.42	4.7	0.76			96			40			30	23	
3.0	Rest		95	11	15.7	0.48	0.64	6.7	0.75			96			40			31	23	
3.5	Unloaded		90	30	12.8	0.40	0.52	5.8	0.77			95			41			26	20	
4.0	Unloaded		95	15	18.0	0.53	0.64	6.7	0.83			103			38			32	26	
4.5	Unloaded		87	17	12.1	0.37	0.48	5.5	0.77			98			40			29	22	
5.0	Unloaded	174/81	89	13	16.6	0.52	0.63	7.1	0.83	7.41	22	99	90	18	39	36	–3	30	25	0.18
5.5	20		90	18	14.8	0.44	0.53	5.9	0.83			103			39			30	25	
6.0	20		93	13	13.1	0.40	0.49	5.3	0.82			98			40			30	24	
6.5	40		98	12	18.2	0.61	0.75	7.7	0.81			94			41			28	23	
7.0	40	192/84	104	15	19.4	0.66	0.83	8.0	0.80	7.40	23	95	86	19	42	37	–5	27	22	0.14
7.5	60		109	14	22.9	0.79	0.94	8.6	0.84			97			42			27	23	
8.0	60		112	13	23.0	0.82	0.93	8.3	0.88			98			43			27	24	
8.5	80		116	17	29.6	1.02	1.11	9.6	0.92			101			41			28	25	
9.0	80	204/90	123	20	33.4	1.09	1.14	9.3	0.96	7.39	23	104	97	14	41	38	–3	29	28	0.21
9.5	100		129	19	39.9	1.28	1.20	9.3	1.07			109			39			30	32	
10.0	100		134	21	40.5	1.37	1.38	10.3	0.99			100			44			28	28	
10.5	120		143	24	42.4	1.30	1.20	8.4	1.08			101			43			31	34	
11.0	120	222/99	143	25	59.6	1.70	1.41	9.9	1.21	7.42	18	117	115	10	35	29	–6	34	41	0.12
11.5	140		146	23	53.6	1.59	1.36	9.3	1.17			104			44			32	38	
12.0	140		146	32	75.1	1.92	1.45	9.9	1.32			119			35			38	50	
12.5	Recovery	210/72	119	25	57.4	1.69	1.38	11.6	1.22			116			37			33	40	
13.0	Recovery		105	22	48.0	1.48	1.12	10.7	1.32			115			39			31	41	
13.5	Recovery		99	20	41.9	1.24	0.85	8.6	1.46			119			38			32	47	
14.0	Recovery		97	21	37.0	1.09	0.77	7.9	1.42	7.34	16	119	119	7	37	31	–6	32	46	0.13
14.5	Recovery		93	26	28.2	0.85	0.61	6.6	1.39			116			40			31	43	
15.0	Recovery		86	19	29.2	0.83	0.55	6.4	1.51			122			35			33	50	
15.5	Recovery		88	25	19.8	0.58	0.41	4.7	1.41			117			39			30	43	

(branch point 3.3) was abnormal, directing us to a diagnosis of myocardial ischemia. This is consistent with the patient's chest pain and low $\Delta\dot{V}O_2/\Delta WR$; even more significant is the plateau in $\dot{V}O_2$ and O_2 pulse that occurred concurrently with the onset of abnormal ST-segment changes. The transient rise in O_2 pulse after heavy exercise ceased, which is evidence for recovery of stroke volume from ischemia-induced left ventricular dysfunction as blood pressure, heart rate, and therefore myocardial oxygen demand fell in recovery. Of note, if exercise had been terminated at 85% of the predicted maximal heart rate (140 bpm), the key abnormalities would not have been evident.

Conclusion

This patient had myocardial ischemia secondary to coronary artery disease. Untreated systemic hypertension undoubtedly contributed to the occurrence of angina.

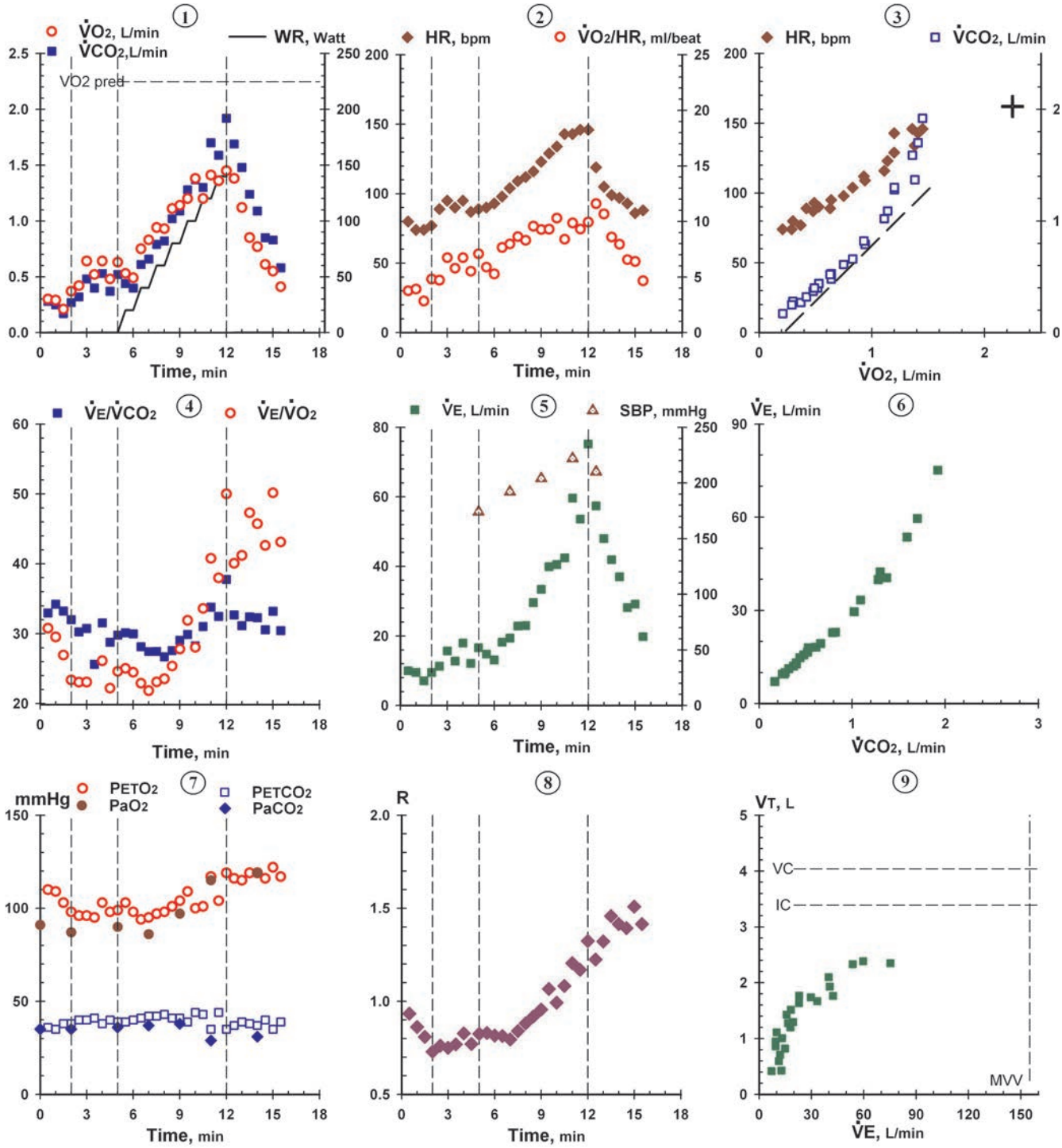

FIGURE 10.16.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 17 Myocardial Ischemia: Atypical Chest Pain

CLINICAL FINDINGS

A 61-year-old retired man complained of breathing difficulties that he could not quantify or describe well. He denied shortness of breath but stated that he stopped using stairs because of a "peculiar feeling in his chest." He also complained of a stabbing substernal and right flank pain not associated with exertion or stress and of neck pain associated with movement of the head attributed to degenerative cervical spine arthritis. He had never smoked cigarettes. Examination revealed psoriasis and normal blood pressure, heart sounds, and peripheral pulses. He had ECG findings suggestive of left ventricular hypertrophy.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 20 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of shortness of breath and tired thighs. He denied chest pain. The ECG developed slight ST-segment depression in leads II, III, aVF, V_5, and V_6 at 120 W of exercise (HR 150), which progressed to maximum ST depression of 5 mm at the cessation of exercise (180 W). Rare, unifocal, premature ventricular contractions were noted. The ECG returned to baseline after 14 minutes of recovery.

Table 10.17.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		61
Sex		Male
Height (cm)		176
Weight (kg)	78	70
Hematocrit (%)		39
VC (L)	4.23	3.95
IC (L)	2.82	2.60
TLC (L)	6.47	6.01
FEV_1 (L)	3.32	3.25
FEV_1/VC (%)	78	82
MVV (L/min)	137	121
DLCO (mL/mm Hg/min)	25.5	33.3

INTERPRETATION

Comments

Resting respiratory function (Table 10.17.1) and ECG were normal.

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and anaerobic threshold were normal (Tables 10.17.2 and 10.17.3 and Fig. 10.17.1), which directs us through branch point 1.1 to Flowchart 2 (Fig. 8.2). The ECG was abnormal and

Table 10.17.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.08	1.90
Maximum heart rate (beats/min)	159	180
Maximum O_2 pulse (mL/beat)	13.1	10.6
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	7.5
AT (L/min)	>0.91	1.1
Blood pressure (mm Hg [rest, max])		144/75, 246/108
Maximum $\dot{V}E$ (L/min)		86
Exercise breathing reserve (L/min)	>15	35
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.1	27.1
PaO_2 (mm Hg [rest, max ex])		87, 103
$P(A-a)O_2$ (mm Hg [rest, max ex])		5, 15
$PaCO_2$ (mm Hg [rest, max ex])		41, 40
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		2, –1
VD/VT (rest, heavy ex)		0.48, 0.24
HCO_3^- (mEq/L [rest, 2-min recov])		26, 20

Table 10.17.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	144/75								7.48	26		106			36				
0.5	Rest		66	20	7.4	0.12	0.17	2.6	0.71			104			37			48	34	
1.0	Rest		67	16	9.1	0.19	0.27	4.0	0.70			101			37			41	29	
1.5	Rest		68	19	11.9	0.28	0.42	6.2	0.67			93			41			37	24	
2.0	Rest		70	14	7.6	0.13	0.20	2.9	0.65	7.44	27	37	87	5	39	41	2	49	32	0.48
2.5	Rest		70	15	7.9	0.13	0.17	2.4	0.76			101			37			51	39	
3.0	Rest	150/75	70	15	13.2	0.28	0.40	5.7	0.70			91			42			43	30	
3.5	Unloaded		84	14	8.5	0.23	0.35	4.2	0.66			90			43			32	21	
4.0	Unloaded		88	17	13.2	0.34	0.52	5.9	0.65			90			42			35	23	
4.5	Unloaded		85	21	15.4	0.37	0.58	6.8	0.64			91			42			37	23	
5.0	Unloaded		86	17	14.2	0.39	0.59	6.9	0.66			89			43			33	22	
5.5	Unloaded		89	15	17.7	0.55	0.80	9.0	0.69			86			44			30	21	
6.0	Unloaded	171/78	88	17	15.0	0.43	0.63	7.2	0.68	7.41	29	90	83	4	45	46	1	32	22	0.37
6.5	20		95	20	17.2	0.54	0.76	8.0	0.71			91			45			29	20	
7.0	20		93	19	17.9	0.52	0.68	7.3	0.76			95			44			31	24	
7.5	40		95	15	17.6	0.60	0.78	8.2	0.77			93			46			27	21	
8.0	40	192/78	102	17	24.3	0.85	1.03	10.1	0.83	7.40	29	94	83	11	45	48	3	27	22	0.31
8.5	60		104	17	26.0	0.90	1.02	9.8	0.88			97			46			27	24	
9.0	60		105	22	26.9	0.92	1.05	10.0	0.88			97			46			27	24	
9.5	80		122	32	34.2	1.14	1.18	9.7	0.97			102			46			28	27	
10.0	80	216/87	127	25	36.1	1.26	1.29	10.2	0.98	7.40	28	101	94	9	47	46	–1	27	26	0.29
10.5	100		132	27	40.8	1.39	1.31	9.9	1.06			107			44			28	29	
11.0	100		136	28	37.4	1.35	1.30	9.6	1.04			102			48			26	27	
11.5	120		144	29	51.4	1.78	1.58	11.0	1.13			107			45			27	31	
12.0	120	231/96	150	33	50.8	1.77	1.50	10.0	1.18	7.39	27	108	98	12	46	45	–1	27	32	0.28
12.5	140		156	30	58.1	2.04	1.69	10.8	1.21			110			44			27	33	
13.0	140		168	34	63.3	2.13	1.74	10.4	1.22			111			44			28	35	
13.5	160		172	35	72.8	2.38	1.84	10.7	1.29			113			43			29	38	
14.0	160	234/99	178	34	76.0	2.53	1.90	10.7	1.33	7.39	24	117	103	15	41	40	–1	29	38	0.24
14.5	180	246/108	180	47	85.5	2.62	1.85	10.3	1.42			118			41			31	44	
15.0	Recovery		171	35	71.3	2.46	1.90	11.1	1.29			114			43			28	36	
15.5	Recovery		160	36	66.6	2.15	1.45	9.1	1.48			118			41			30	44	
16.0	Recovery		143	20	47.5	1.53	1.03	7.2	1.49			116			43			30	44	
16.5	Recovery	192/78	135	29	49.6	1.51	1.00	7.4	1.51	7.30	20	117	107	13	42	41	–1	31	47	0.31

the O_2 pulse was reduced, reaching a plateau for the last 5 minutes of incremental exercise (panel 2, Fig. 10.17.1) (branch point 2.1, Fig. 8.2). The indices of ventilation–perfusion matching were normal (branch point 2.3). The low O_2 pulse, steep heart rate–$\dot{V}O_2$ relationship, and reduced $\dot{V}O_2/\Delta WR$ indicate that the ST-segment changes were functionally significant—that is, they were consistent with the development of myocardial dysfunction due to exercise-induced ischemia.

Conclusion

This patient with atypical chest pain experienced exercise-induced myocardial ischemia.

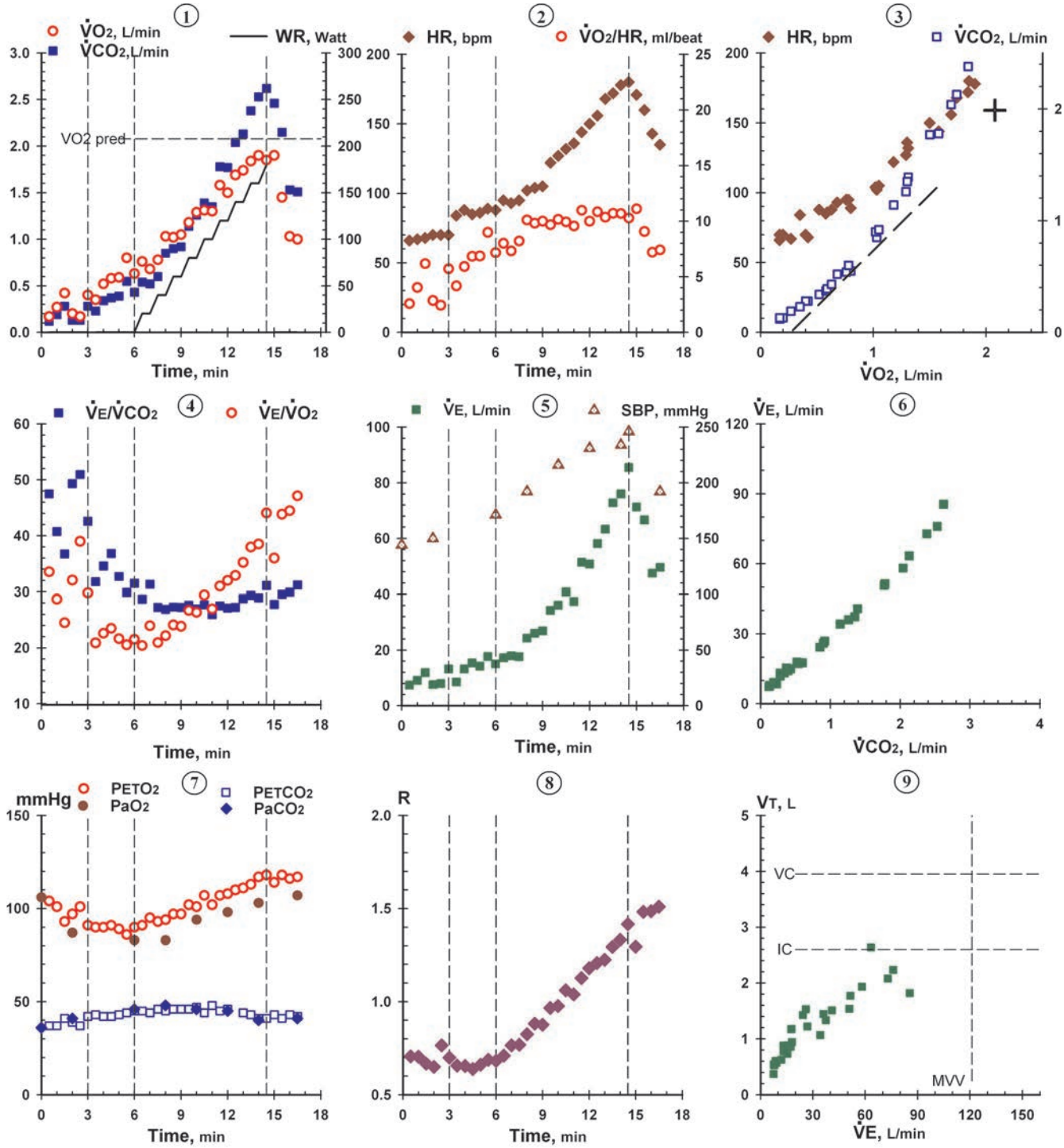

FIGURE 10.17.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 18 Myocardial Ischemia: Small Vessel Disease

CLINICAL FINDINGS

A 47-year-old asymptomatic man was referred for cardiopulmonary exercise testing because of a strong family history of coronary artery disease and the finding of coronary artery calcification on an ultrafast computed tomographic (CT) cardiac scan. Physical examination, chest radiographs, and resting ECGs were normal.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 25 W per minute to tolerance. Heart rate and rhythm were continuously monitored; 12-lead ECGs were obtained during rest, exercise, and recovery. Blood pressure was measured with a sphygmomanometer and oxygen saturation with pulse oximeter. The patient appeared to give an excellent effort and stopped exercise because of leg fatigue. He denied chest pain during or after the study. ECGs showed progressive downsloping ST-segment depression in leads II, III, aVF, and V_3 to V_6 after 150 W of exercise, which reached approximately 3 mm in leads II and V_4 at the cessation of exercise. These changes resolved by 5 minutes of recovery; there was no ectopy.

INTERPRETATION

Comments

Spirometry was normal (Table 10.18.1).

Table 10.18.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		47
Sex		Male
Height (cm)		175
Weight (kg)	78	64
Hematocrit (%)		42
VC (L)	4.78	5.04
IC (L)	3.19	3.70
FEV_1 (L)	3.91	4.03
FEV_1/VC (%)	81	80
MVV (L/min)	153	180

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ was reduced, but the anaerobic threshold was within normal limits (Tables 10.18.2 and 10.18.3 and Fig. 10.18.1). Proceeding next to Flowchart 3 (Fig. 8.3), the high breathing reserve (branch point 3.1) and abnormal ECG that developed during exercise (branch point 3.3) lead to the diagnosis of myocardial ischemia. The low O_2 pulse and failure of $\dot{V}O_2$ and O_2 pulse to rise appropriately for the last 2.5 minutes of exercise indicate that an O_2 delivery problem developed at that time. The constant O_2 pulse indicates that the product of the arterial–mixed venous O_2 content difference and stroke volume reached its maximum value prematurely. This constant value might reflect a decreasing stroke volume while arteriovenous difference is increasing.

Conclusion

The abrupt change in a previously normal pattern of utilization of O_2 (normal $\Delta\dot{V}O_2/\Delta WR$) after which $\dot{V}O_2$ fails to keep pace with increasing work rate suggests exercise-induced myocardial ischemia. The combination of O_2 delivery abnormalities (which imply a failure of cardiac output to increase appropriately for the work rate) and ECG findings consistent with myocardial ischemia suggests that the patient had functionally important coronary artery disease. Follow-up coronary angiograms showed diffuse distal coronary artery disease not amenable to bypass. The patient was treated medically.

Table 10.18.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.35	1.68
Maximum heart rate (beats/min)	173	181
Maximum O_2 pulse (mL/beat)	13.6	10.4
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	6.4
AT (L/min)	>1.01	1.3
Blood pressure (mm Hg [rest, max])		125/82, 160/90
Maximum $\dot{V}E$ (L/min)		78
Exercise breathing reserve (L/min)	>15	102
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.6	19.6
O_2 saturation, oximeter (rest, max)		99, 95

Table 10.18.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	125/82																		
0.5	Rest		86	11	5.4	0.15	0.21	2.4	0.71			89			44			30	21	
1.0	Rest		89	14	3.4	0.06	0.09	1.0	0.67			86			46			37	25	
1.5	Rest		80	10	6.0	0.20	0.29	3.6	0.69			83			47			26	18	
2.0	Rest	110/60	80	8	3.6	0.09	0.13	1.6	0.69			90			46			32	22	
2.5	Rest		81	12	4.6	0.14	0.19	2.3	0.74			91			46			26	19	
3.0	Rest		98	8	4.6	0.14	0.16	1.6	0.88			89			47			28	25	
3.5	Unloaded		105	12	9.2	0.36	0.43	4.1	0.84			87			49			23	19	
4.0	Unloaded		103	12	9.5	0.35	0.46	4.5	0.76			89			48			24	18	
4.5	Unloaded		103	14	11.0	0.41	0.51	5.0	0.80			90			48			24	19	
5.0	Unloaded		105	12	11.9	0.47	0.56	5.3	0.84			90			48			23	19	
5.5	Unloaded		105	17	9.7	0.37	0.45	4.3	0.82			87			51			22	18	
6.0	Unloaded	120/82	106	13	12.2	0.48	0.56	5.3	0.86			93			49			23	20	
6.5	25		106	13	8.0	0.32	0.37	3.5	0.86			89			52			22	19	
7.0	20		109	12	13.6	0.55	0.59	5.4	0.93			95			50			23	21	
7.5	50		114	12	14.1	0.61	0.63	5.5	0.97			92			51			21	21	
8.0	50	130/90	119	13	16.3	0.70	0.75	6.3	0.93			93			51			22	20	
8.5	75		122	14	17.3	0.77	0.84	6.9	0.92			92			52			21	19	
9.0	75		131	14	18.7	0.88	0.88	6.7	1.00			92			53			20	20	
9.5	100		137	16	22.2	1.05	1.09	8.0	0.96			92			54			20	19	
10.0	100	130/90	140	15	23.3	1.13	1.19	8.5	0.95			91			55			19	19	
10.5	125		145	17	26.3	1.20	1.24	8.6	0.97			94			55			21	20	
11.0	125		152	17	29.5	1.47	1.35	8.9	1.09			95			56			19	21	
11.5	150		158	18	32.8	1.66	1.50	9.5	1.11			95			56			19	21	
12.0	150	145/90	163	19	37.7	1.88	1.56	9.6	1.21			100			55			19	23	
12.5	175		167	22	44.8	2.13	1.73	10.4	1.23			101			55			20	25	
13.0	175		169	22	45.1	2.23	1.76	10.4	1.27			102			56			19	25	
13.5	200		173	22	53.4	2.52	1.85	10.7	1.36			103			54			20	28	
14.0	200	160/90	176	26	62.5	2.76	1.87	10.6	1.48			111			49			22	32	
14.5	225		181	32	77.5	3.00	1.87	10.3	1.60			113			48			25	40	
15.0	225		181	31	77.8	2.95	1.88	10.4	1.57			113			47			25	40	
15.5	Recovery		167	22	53.4	2.37	1.62	9.7	1.46			110			50			22	32	
16.0	Recovery		152	21	40.2	1.71	1.06	7.0	1.61			114			48			22	36	
16.5	Recovery		140	20	39.1	1.57	0.92	6.6	1.71			116			47			24	41	
17.0	Recovery	160/75	131	17	28.9	1.10	0.59	4.5	1.86			120			44			25	47	

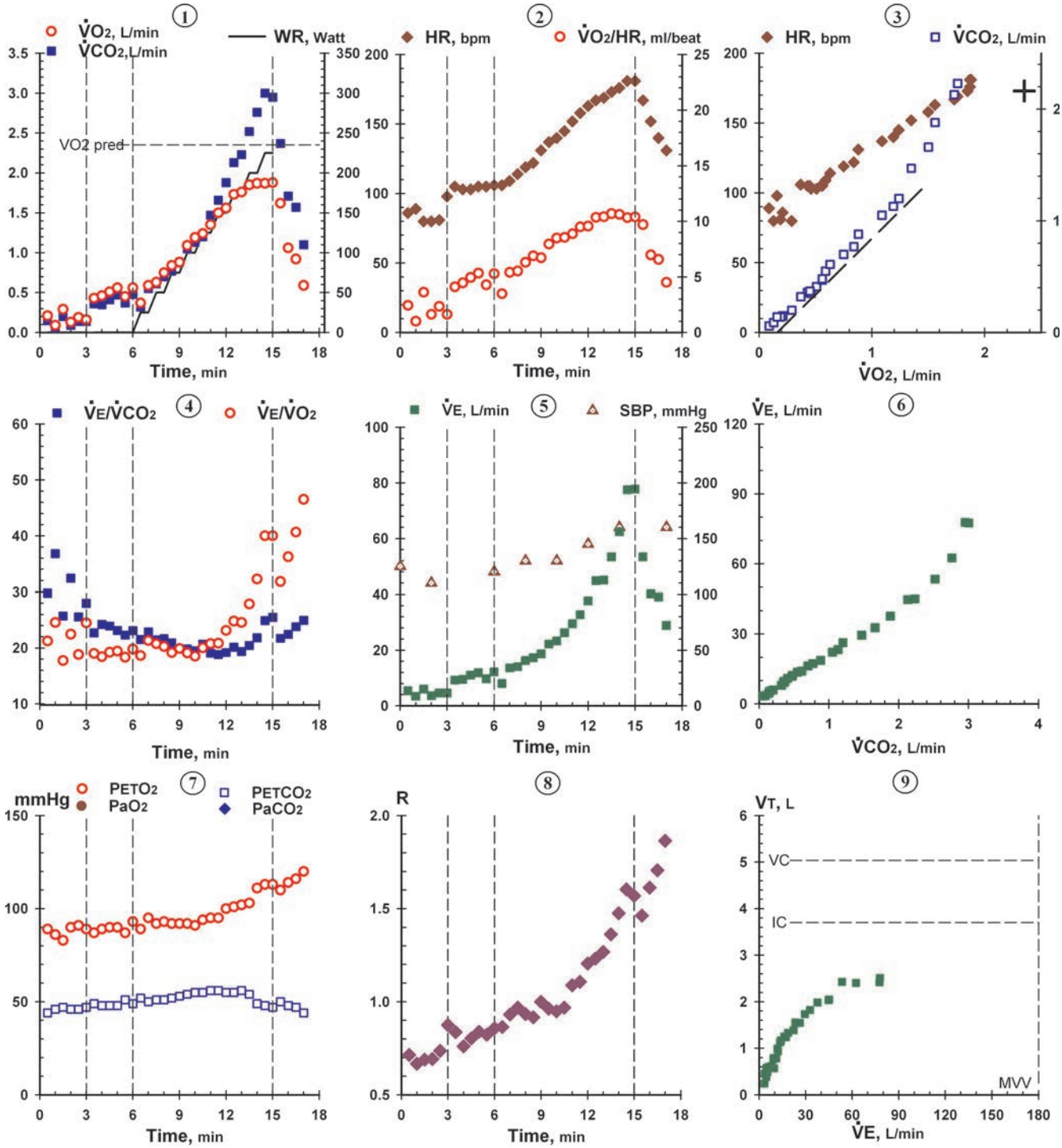

FIGURE 10.18.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 25 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 19 Myocardial Ischemia: Interim Development of Coronary Artery Disease over 3 Years

CLINICAL FINDINGS

A 57-year-old male asbestos worker was evaluated at a 3-year interval. When first evaluated, he had a several-year history of diabetes mellitus treated with insulin, hypertension treated with hydrochlorothiazide, obesity, arthritis of the hip, and moderate exertional dyspnea. He had never smoked tobacco. Examination at that time revealed moderate obesity and minimal pleural thickening on his chest radiographs. The respiratory function and exercise study data of that evaluation are shown in Tables 10.19.1 to 10.19.3 and Figure 10.19.1. When evaluated 3 years later (Tables 10.19.4 to 10.19.6 and Fig. 10.19.2), he was being treated with cimetidine for symptoms of "gas" pain in his left anterior chest associated with exercise.

EXERCISE FINDINGS

On both occasions, the patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 2 or 3 minutes. The work rate was then increased 20 W per minute to tolerance. On the first occasion, arterial blood was sampled every second minute and intra-arterial pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of thigh pain, without chest or abdominal pain. No ECG abnormalities were noted at rest, but during high work levels, 1- to 2-mm J-point depression with upsloping ST segments was seen in a few leads.

On the second exercise test, the patient stopped exercise because of calf fatigue and an inability to maintain his cycling frequency. During the last 1 to 2 minutes of exercise, he noted left parasternal nonradiating "gas" pain, typical of his recent symptoms, which subsided within 3 minutes of recovery. He denied shortness of breath. The resting ECG was normal. However, at 120 W, 1.5 mm of ST-segment depression was evident in leads II, III, aVF, V_3, and V_4; by 140 W, the ST depression had progressed to 2.5 to 3 mm and had extended to include V_5 and V_6. The ECG returned to normal by 3 minutes after exercise.

Table 10.19.1

Selected Respiratory Function Data: First Study

Measurement	Predicted	Measured
Age (years)		57
Sex		Male
Height (cm)		171
Weight (kg)	74	96
Hematocrit (%)		46
VC (L)	3.99	4.25
IC (L)	2.66	3.37
TLC (L)	6.03	6.00
FEV_1 (L)	3.14	3.52
FEV_1/VC (%)	79	83
MVV (L/min)	134	135
D_{LCO} (mL/mm Hg/min)	26.4	36.4

Table 10.19.2

Selected Exercise Data: First Study

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.32	2.20
Maximum heart rate (beats/min)	163	148
Maximum O_2 pulse (mL/beat)	14.2	14.9
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	10.3
AT (L/min)	>1.02	1.2
Blood pressure (mm Hg [rest, max])		156/94, 250/113
Maximum $\dot{V}E$ (L/min)		143
Exercise breathing reserve (L/min)	>15	−8
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.8	28.8
PaO_2 (mm Hg [rest, max ex])		100, 129
$P(A-a)O_2$ (mm Hg [rest, max ex])		10, 3
$PaCO_2$ (mm Hg [rest, max ex])		35, 23
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		−4, −2
V_D/V_T (rest, heavy ex)		0.16, 0.19
HCO_3^- (mEq/L [rest, 2-min recov])		24, 15

Table 10.19.3

First Study

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	156/94								7.37	24		84			43				
1.0	Rest		80	10	11.9	0.36	0.40	5.0	0.90			109			36			31	28	
1.5	Rest		85	11	10.0	0.32	0.39	4.6	0.82			103			39			28	23	
2.0	Rest		87	7	9.4	0.30	0.36	4.1	0.83			104			39			29	24	
2.5	Rest	175/100	84	7	10.1	0.32	0.38	4.5	0.84	7.40	21	105	100	10	39	35	–4	30	25	0.16
3.0	Unloaded		97	21	21.8	0.65	0.85	8.8	0.76			94			43			31	24	
3.5	Unloaded		96	18	17.4	0.55	0.74	7.7	0.74			99			40			29	21	
4.0	Unloaded		100	22	23.7	0.77	1.01	10.1	0.76			99			40			28	22	
4.5	Unloaded	206/113	98	21	20.8	0.63	0.71	7.2	0.89	7.41	19	105	103	13	40	31	–9	30	27	0.07
5.0	20		101	21	28.3	0.91	1.01	10.0	0.90			104			39			29	26	
5.5	20		101	20	29.2	0.92	1.02	10.1	0.90			106			39			30	27	
6.0	40		102	16	29.4	0.96	1.07	10.5	0.90			104			40			29	26	
6.5	40	219/106	108	20	26.3	0.89	1.04	9.6	0.86	7.39	21	103	100	9	40	36	–4	28	24	0.12
7.0	60		111	21	30.3	1.01	1.14	10.3	0.89			104			41			28	25	
7.5	60		115	22	35.2	1.17	1.22	10.6	0.96			107			40			28	27	
8.0	80		117	25	40.7	1.36	1.36	11.6	1.00			110			39			28	28	
8.5	80	238/106	129	26	45.7	1.50	1.41	10.9	1.06	7.39	21	112	103	13	39	36	–3	29	31	0.16
9.0	100		123	28	50.9	1.65	1.53	12.4	1.08			114			38			29	32	
9.5	100		125	29	51.9	1.70	1.56	12.5	1.09			114			38			29	32	
10.0	120		127	32	67.8	2.02	1.68	13.2	1.20			119			35			32	39	
10.5	120	250/113	131	39	80.3	2.24	1.84	14.0	1.22	7.41	19	122	114	9	32	31	–1	34	42	0.18
11.0	140		131	41	91.5	2.42	1.99	15.2	1.22			120			34			36	44	
11.5	140		141	55	121.3	2.79	2.15	15.2	1.30			128			27			42	54	
12.0	160	235/110	148	59	142.8	2.95	2.20	14.9	1.34	7.42	15	130	129	3	25	23	–2	47	63	0.19
12.5	Recovery		131	39	80.8	2.04	1.73	13.2	1.18			124			30			38	45	
13.0	Recovery		119	33	50.4	1.18	0.98	8.2	1.20			127			27			40	49	

INTERPRETATION

Comments

Resting respiratory function studies and arterial blood gases and pH were normal at both evaluations.

Analysis

Referring to Flowchart 1 (Fig. 8.1), in the first study, all findings were normal with the exception of a negative breathing reserve, which we interpret as indicating the patient's sensitive ventilatory response to the exercise-induced metabolic acidosis with precise pH regulation. To maintain this normal pH, he lowered his Pa_{CO_2} from 35 to 23 mm Hg over a 3.5-minute period. He had no evidence of pulmonary or cardiovascular dysfunction.

In the second study, 3 years later, the peak $\dot{V}_{O_2}$ was reduced while the anaerobic threshold, although lower than that of the earlier study, remained within the normal range (Table 10.19.5). Referring to Flowchart 3 (Fig. 8.3), the breathing reserve was normal (branch point 3.1). The ECG during the second exercise study was clearly abnormal, leading to the diagnosis of myocardial ischemia. The flattening of $\Delta\dot{V}_{O_2}/\Delta WR$ and flat O_2 pulse during increasing work rate are consistent with the diagnosis of myocardial ischemia.

Conclusion

This patient, with risk factors for coronary artery disease, initially had a normal cardiovascular response to incremental exercise. Three years later, his O_2 flow became abnormal during incremental exercise coincident with ECG abnormalities and chest pain. These findings strongly supported the diagnosis of myocardial ischemia.

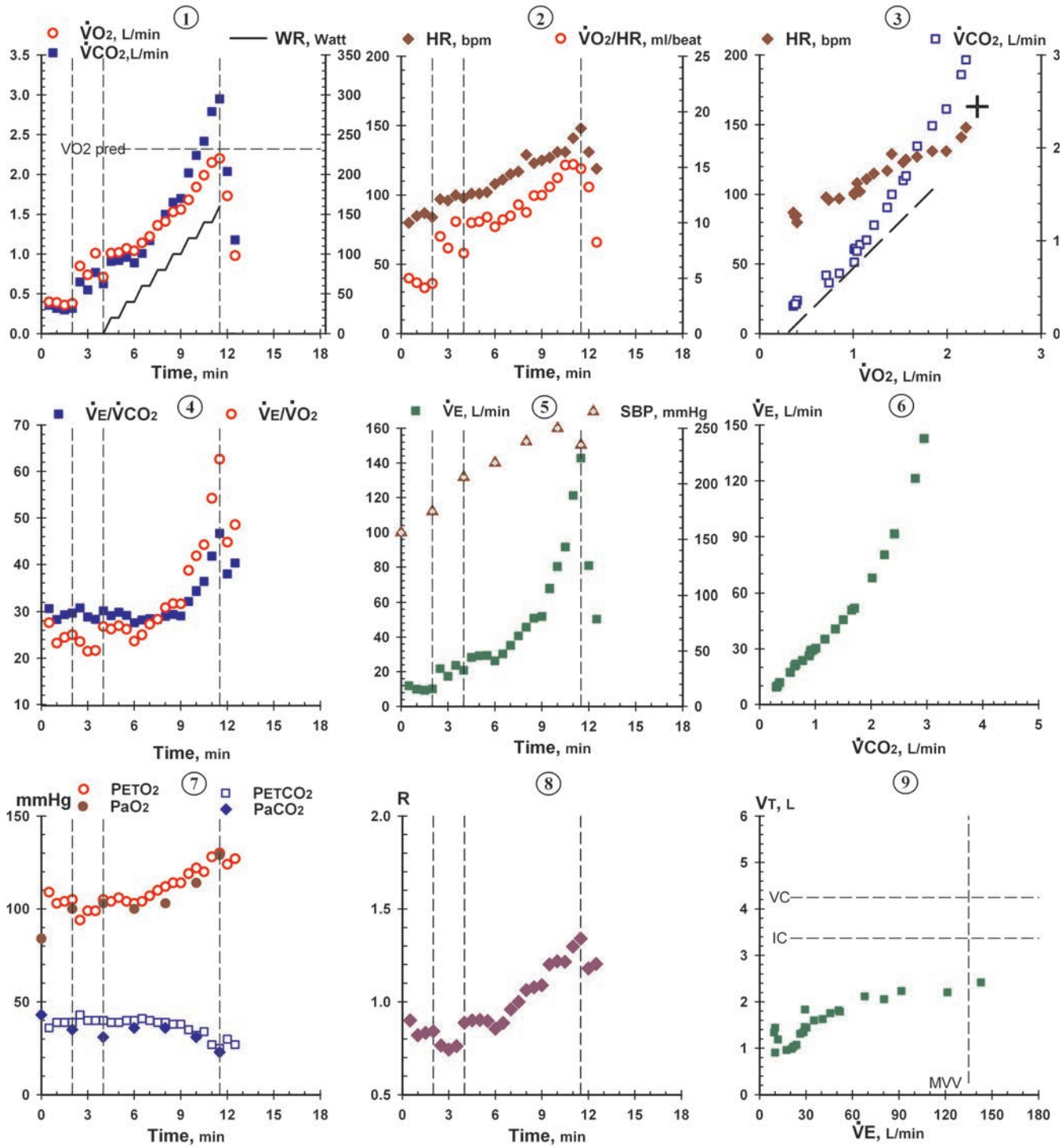

FIGURE 10.19.1. First study, age 57. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.19.4

Selected Respiratory Function Data: Second Study

Measurement	Predicted	Measured
Age (years)		60
Sex		Male
Height (cm)		171
Weight (kg)	74	87
VC (L)	3.92	4.38
IC (L)	2.61	2.53
TLC (L)	6.11	5.87
FEV_1 (L)	3.06	3.59
FEV_1/VC (%)	78	81
MVV (L/min)	132	158
DLCO (mL/mm Hg/min)	26.4	31.8

Table 10.19.5

Selected Exercise Data: Second Study

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.19	1.63
Maximum heart rate (beats/min)	160	118
Maximum O_2 pulse (mL/beat)	13.7	14.2
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	6.8
AT (L/min)	>0.96	1.05
Blood pressure (mm Hg [rest, max])		140/80, 210/100
Maximum $\dot{V}E$ (L/min)		79
Exercise breathing reserve (L/min)	>15	79
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.1	28.3

Table 10.19.6

Second Study

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg ET	Po_2, mm Hg a	Po_2, mm Hg (A − a)	Pco_2, mm Hg ET	Pco_2, mm Hg a	Pco_2, mm Hg (a − ET)	$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{VD}{VT}$
	Rest	140/80																		
0.5	Rest		59	12	9.1	0.25	0.31	5.3	0.81			102			39			32	26	
1.0	Rest	140/900	57	12	9.6	0.25	0.29	5.1	0.86			106			37			34	30	
1.5	Rest		54	13	6.2	0.13	0.15	2.8	0.87			104			38			39	34	
2.0	Rest	140/90	55	15	7.7	0.16	0.22	4.0	0.73			99			39			40	39	
2.5	Rest		57	13	10.5	0.28	0.37	6.5	0.76			99			39			34	25	
3.0	Rest		57	19	10.8	0.27	0.34	6.0	0.79			101			39			34	27	
3.5	Unloaded		70	18	16.8	0.56	0.70	10.0	0.80			100			41			27	22	
4.0	Unloaded		70	13	16.7	0.52	0.58	8.3	0.90			108			38			30	27	
4.5	Unloaded		70	14	17.0	0.56	0.66	9.4	0.85			104			39			28	24	
5.0	Unloaded		72	19	21.3	0.65	0.69	9.6	0.94			109			38			30	29	
5.5	Unloaded		72	19	19.8	0.63	0.73	10.1	0.86			103			40			29	25	
6.0	Unloaded	145/90	76	16	21.2	0.68	0.80	10.5	0.85			100			41			29	25	
6.5	20		76	13	18.0	0.59	0.66	8.7	0.89			106			39			29	26	
7.0	20		76	15	19.9	0.66	0.76	10.0	0.87			103			40			28	25	
7.5	40		76	16	21.8	0.74	0.87	11.4	0.85			102			41			28	23	
8.0	40	180/90	83	19	28.2	0.92	0.98	11.8	0.94			104			41			29	27	
8.5	60		85	17	27.1	0.95	1.06	12.5	0.90			102			42			27	24	
9.0	60		88	20	36.8	1.23	1.23	14.0	1.00			102			42			29	29	
9.5	80		93	24	37.4	1.25	1.18	12.7	1.06			109			41			28	30	
10.0	80	195/85	100	23	42.1	1.38	1.26	12.6	1.10			113			38			29	32	
10.5	100		102	25	48.4	1.53	1.36	13.3	1.13			114			38			30	34	
11.0	100		105	29	57.6	1.72	1.42	13.5	1.21			118			35			32	39	
11.5	120		103	34	68.8	1.92	1.50	14.6	1.28			121			33			34	44	
12.0	120	210/100	113	49	79.3	2.02	1.54	13.6	1.31			121			33			37	49	
12.5	140		118	40	78.0	2.06	1.58	13.4	1.30			119			34			36	47	
13.0	140		115	42	76.5	2.16	1.63	14.2	1.33			119			33			34	45	
13.5	Recovery		98	27	66.8	1.89	1.35	13.8	1.40			120			34			34	48	
14.0	Recovery	210/90	97	27	61.9	1.71	1.23	12.7	1.39			123			32			35	48	
14.5	Recovery		91	23	45.5	1.27	0.94	10.3	1.35			122			33			34	46	
15.0	Recovery	180/90	91	23	41.9	1.16	0.88	9.7	1.32			122			33			34	45	

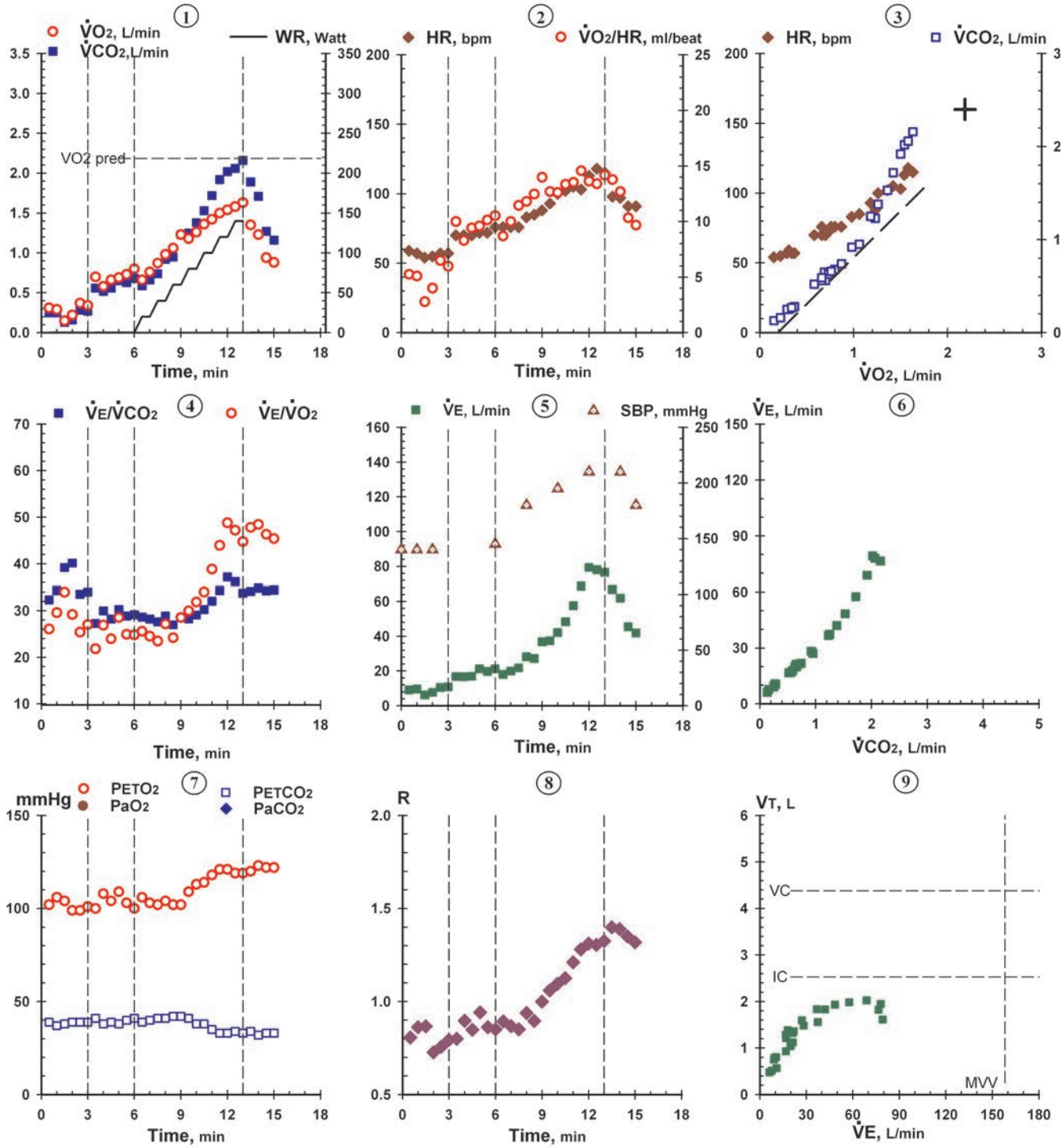

FIGURE 10.19.2. Second study, age 60. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 20 Myocardial Ischemia: Coronary Artery Disease in a Previously Athletic Man

A healthy 65-year-old man (previously described in Case 9 of this chapter) enjoyed hiking in the mountains and had normal exercise findings with above-average exercise capacity. Seven years later, at age 72, he still enjoyed hiking, although he no longer did so at high altitude. He had returned to his cardiologist complaining that he had fatigue with exertion and could no longer keep pace when walking with his female companion. An exercise echocardiogram study was done without gas exchange measurements and reportedly showed ST-segment depression in the left precordial leads and a run of three premature ventricular contractions (PVCs) near the end of the test. The estimated pulmonary artery pressure during exercise by echocardiography was 70 mm Hg. Because the patient's overall exercise tolerance was good and the echocardiogram was otherwise normal, the ECG changes were discounted as a "false-positive ECG response." However, because of the suggestion of possible pulmonary hypertension, the patient was referred to a pulmonologist. Pulmonary function tests and a $\dot{V}/\dot{Q}$ scan revealed no abnormalities to account for the echocardiogram findings and the patient was referred for cardiopulmonary exercise testing for further evaluation.

EXERCISE FINDINGS

The patient was tested using the same protocol as that used in his initial evaluation at age 65, including arterial blood sampling and blood pressure measurements. After 3 minutes of rest and 3 minutes of unloaded cycling, work rate increased by 20 W per minute until symptomatic maximum. On ECG monitoring, there was ST-segment depression in leads aVF, III, and V_5, first noted at a heart rate of around 125 bpm and progressing to a maximum of 2 mm at a heart rate of 137 bpm. He had no ectopic beats or chest pain and the repolarization abnormalities resolved in the recovery period.

INTERPRETATION

Comments

Resting respiratory function studies were normal (Table 10.20.1).

Table 10.20.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		72
Sex		Male
Height (cm)		184
Weight (kg)	83	84
Hematocrit (%)		47
VC (L)	4.61	4.39
IC (L)	3.08	3.82
FEV_1 (L)	3.29	2.94
FEV_1/VC (%)	75	68
MVV (L/min)	134	130
D_{LCO} (mL/mm Hg/min)	27.0	19.2

Analysis

Compared to the study performed at age 65, the predicted peak $\dot{V}O_2$ for this patient had decreased by 0.2 L/min, but his actual peak $\dot{V}O_2$ had decreased by 0.7 L/min (Tables 10.20.2 and 10.20.3 and Figs. 10.20.1 and 10.20.2). Referring to Flowchart 1 (Fig. 8.1), his peak $\dot{V}O_2$ was still within normal limits (branch point 1.1). Referring to Flowchart 2 (Fig. 8.2), his ECG was abnormal (branch point 2.1). His V_D/V_T, $P(A-a)O_2$, and $P(a-ET)CO_2$ were normal (branch point 2.3), indicating that although the patient probably had some cardiovascular disease, he did not have functionally significant impairment in either breathing mechanics or pulmonary gas exchange, making pulmonary vascular disease unlikely, despite the echocardiogram findings.

There were important changes in O_2 transport identified on this test, however, compared to his prior test at age 65. Although the overall slope calculated for the $\dot{V}O_2$–work rate relationship ($\Delta\dot{V}O_2/\Delta WR$) was within the normal range, there was a decrease in this slope over the last 3 minutes of exercise with a coincident steepening of

Table 10.20.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.02	1.99
Maximum heart rate (beats/min)	148	152
Maximum O_2 pulse (mL/beat)	13.6	13.1
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.6
AT (L/min)	>0.95	1.4
Blood pressure (mm Hg [rest, max])		110/60, 200/75
Maximum $\dot{V}E$ (L/min)		85
Exercise breathing reserve (L/min)	>15	46
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.2	30.9
PaO_2 (mm Hg [rest, max ex])		102, 105
$P(A-a)O_2$ (mm Hg [rest, max ex])		15, 21
$PaCO_2$ (mm Hg [rest, max ex])		37, 34
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		5, –2
VD/VT (rest, heavy ex)		0.53, 0.18
HCO_3^- (mEq/L [rest, 2-min recov])		24, 20

the relationship between heart rate and $\dot{V}O_2$ (Fig. 10.20.1 and Fig. 10.20.2, panel 3). This is reflected in the O_2 pulse, which ceased to increase after the heart rate exceeded around 110 bpm, and actually decreased over the final minutes of exercise coincident with the ST-segment changes. It was concluded that the ECG changes reflected functionally important myocardial ischemia. This patient probably developed significant myocardial ischemia starting at a $\dot{V}O_2$ about 1.4 L/min and a heart rate of about 110 bpm (the point at which the heart rate–$\dot{V}O_2$ relationship began to steepen and O_2 pulse no longer increased). Because $C(a-\bar{v})O_2$ increases with increasing $\dot{V}O_2$, the constant O_2 pulse could indicate that the stroke volume was decreasing above the work rate at which the O_2 pulse became constant. A decreasing stroke volume would also be consistent with the nonlinear steepening of the heart rate–$\dot{V}O_2$ relationship as peak $\dot{V}O_2$ was approached (Fig. 10.20.2, panel 3). This is distinctly different from the relationship of heart rate–$\dot{V}O_2$ at age 65 (Panel 3, Fig. 10.20.1).

Conclusion

This man's aerobic function decreased more rapidly than predicted despite his maintenance of an active lifestyle. He had physiologic and ECG evidence of myocardial ischemia during exercise above a $\dot{V}O_2$ of 1.4 L/min and heart rate of 110 bpm. He did not have evidence of significant pulmonary vascular disease, based on the blood gas and VD/VT data during exercise and the normal $\dot{V}E/\dot{V}CO_2$ at the *AT*.

Table 10.20.3

Room Air

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest																			
0.5	Rest		65	24	15.9	0.26	0.21	3.3	1.20			139			29			55	67	
1.0	Rest		65	24	12.9	0.23	0.22	3.4	1.03			134			32			48	50	
1.5	Rest	110/60	65	18	10.6	0.20	0.21	3.3	0.93	7.42	24	130	102	9	33	37	4	46	43	0.43
2.0	Rest		63	21	17.1	0.37	0.39	6.2	0.96			131			33			42	40	
2.5	Rest		72	26	19.3	0.39	0.37	5.2	1.04			136			31			45	46	
3.0	Rest		67	23	18.4	0.35	0.32	4.8	1.08			136			30			48	52	
3.5	Unloaded		75	24	22.0	0.49	0.49	6.5	1.00			132			31			41	41	
4.0	Unloaded		77	17	21.1	0.53	0.51	6.6	1.04			133			33			38	39	
4.5	Unloaded		70	17	24.2	0.58	0.55	7.8	1.06			132			32			39	42	
5.0	Unloaded		69	18	17.3	0.41	0.41	5.9	1.01			133			33			39	39	
5.5	Unloaded		68	21	21.8	0.50	0.46	6.8	1.08			132			31			41	44	
6.0	Unloaded	130/65	66	19	16.2	0.34	0.34	5.2	0.99	7.40	22	135	103	11	33	36	3	44	43	0.41
6.5	7		65	25	19.4	0.40	0.40	6.2	1.00			133			32			43	44	
7.0	18		70	31	19.6	0.39	0.42	6.0	0.93			130			33			44	41	
7.5	29		75	22	21.7	0.54	0.60	8.0	0.90			127			34			37	33	
8.0	39	105/40	76	20	20.5	0.50	0.52	6.8	0.97	7.47	23	129	110	7	34	32	–2	38	37	0.27
8.5	50		77	19	22.5	0.59	0.68	8.8	0.87			125			35			36	31	
9.0	62	105/40	84	20	27.4	0.75	0.85	10.2	0.88	7.41	24	123	97	10	36	39	3	35	30	0.34
9.5	71		86	22	32.4	0.88	0.92	10.7	0.95			127			35			35	33	
10.0	80	120/50	89	23	33.7	0.97	1.07	12.0	0.90	7.42	24	123	103	7	37	37	0	33	30	0.28
10.5	90		99	26	43.9	1.18	1.18	11.9	1.01			129			34			36	36	
11.0	100	115/40	94	23	45.7	1.29	1.31	13.9	0.98	7.41	24	127	99	12	36	39	3	34	34	0.34
11.5	109		101	23	45.5	1.35	1.41	13.9	0.96			125			37			33	31	
12.0	120	135/50	108	25	50.0	1.46	1.47	13.6	0.99	7.43	24	126	107	6	36	37	1	33	33	0.28
12.5	129		111	27	53.9	1.60	1.57	14.1	1.02			127			36			32	33	
13.0	141	145/55	114	25	55.8	1.70	1.65	14.4	1.03	7.42	23	126	106	9	37	36	–1	32	33	0.23
13.5	149		118	24	54.7	1.71	1.63	13.8	1.04			126			38			31	32	
14.0	162	150/55	123	27	61.7	1.91	1.81	14.7	1.05	7.40	22	126	106	9	38	36	–2	31	33	0.23
14.5	169		130	30	71.3	2.10	1.84	14.2	1.14			130			36			33	38	
15.0	177	175/65	136	32	71.2	2.14	1.89	13.9	1.14	7.40	21	129	103	15	37	35	–2	32	36	0.22
15.5	192		143	32	79.1	2.34	1.95	13.7	1.20			132			36			33	39	
16.0	201	180/65	150	32	81.1	2.34	1.94	12.9	1.21	7.40	21	132	100	21	35	34	–1	34	41	0.24
16.5	Recovery		154	29	74.5	2.31	1.95	12.7	1.18	7.39	20	129	105	15	39	34	–5	31	37	0.18
17.0	Recovery		138	29	74.7	2.13	1.47	10.7	1.44			136			36			34	49	
17.5	Recovery		121	30	61.2	1.62	0.97	8.0	1.67			141			34			36	61	
18.0	Recovery		108	32	47.3	1.17	0.70	6.5	1.66			142			32			38	64	
18.5	Recovery		101	27	44.1	1.07	0.67	6.6	1.60			142			31			40	63	

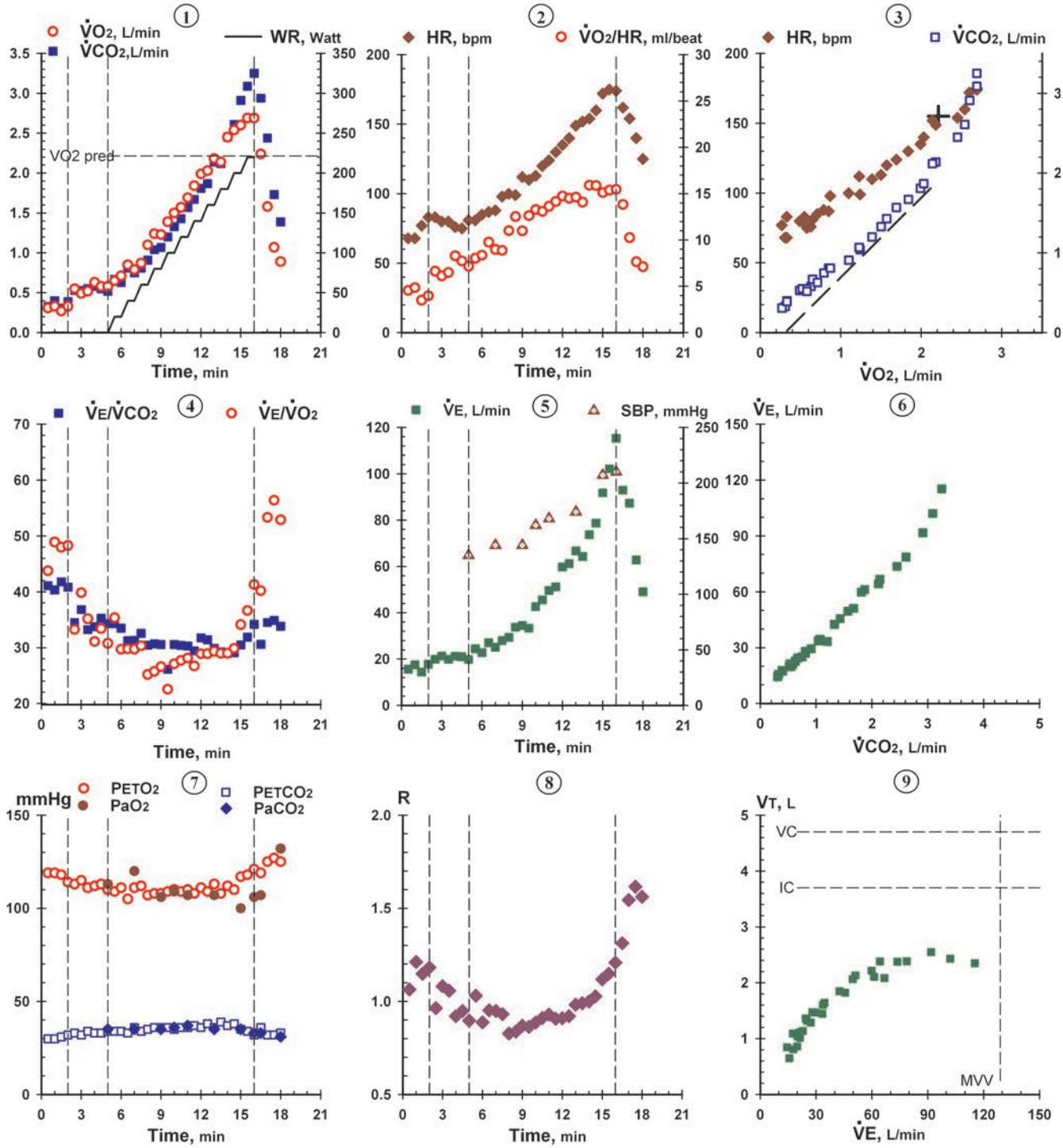

FIGURE 10.20.1. Test performed at age 65. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

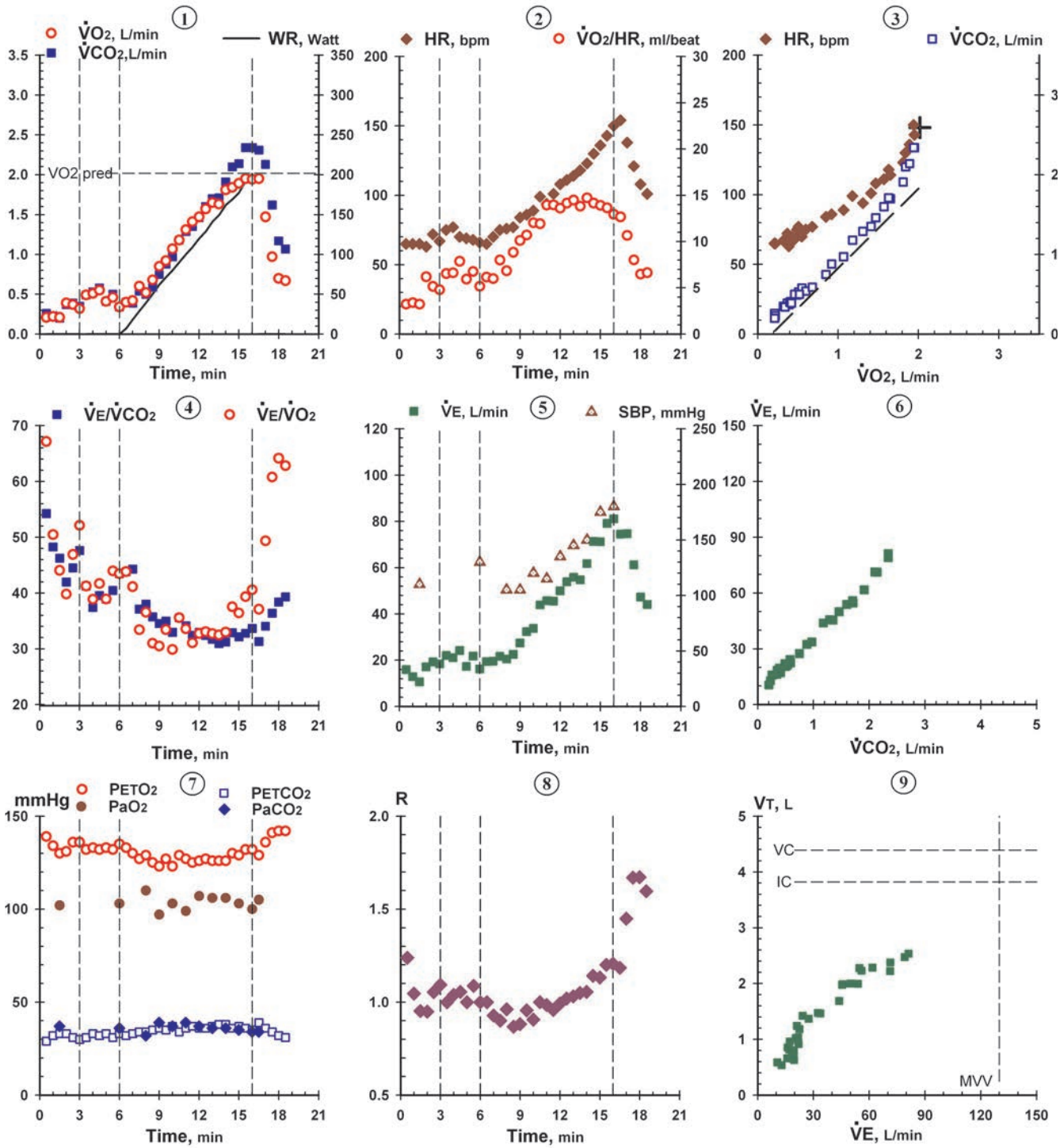

FIGURE 10.20.2. Test performed at age 72. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 21 Peripheral Arterial Disease

CLINICAL FINDINGS

A 65-year-old cigarette-smoking man was evaluated as part of a research study related to coronary artery calcification. He had been overweight and diabetic for approximately 6 years. He had an active lifestyle and walked regularly for exercise but had been limited in his speed of walking for approximately 5 years due to pain in his thighs and calves, especially on the right side. He had some cough and sputum production for a decade. He denied chest pain, shortness of breath, wheezing, edema, or skin problems. Pulses could not be palpated in the legs except for a faint right femoral artery pulse. The patient had no edema; skin warmth and color were good.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 15 W per minute to tolerance. Heart rate and rhythm were continuously monitored; 12-lead ECGs were obtained during rest, exercise, and recovery. Blood pressure was measured with a sphygmomanometer. The patient appeared to give an excellent effort and stopped exercise because of bilateral thigh and calf pain, similar to his usual symptoms. He denied chest pain or discomfort during or after the study. ECGs showed occasional premature ventricular contractions both at rest and during exercise but were otherwise normal. No abnormal ST segments or T waves were noted before, during, or after exercise.

INTERPRETATION

Comments

The patient has mild, asymptomatic airway obstruction (Table 10.21.1), diabetes mellitus, obesity, and clinical evidence of peripheral arterial disease. Of note, his cardiac scan had shown no coronary artery calcification.

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ and the anaerobic threshold were reduced (Table 10.21.2). Proceeding next to Flowchart 4 (Fig. 8.4), the high breathing reserve (branch point 4.1) and normal $\dot{V}E/\dot{V}CO_2$ at the anaerobic threshold (branch point 4.3) lead to the category of "O_2 flow problem of non-pulmonary origin." Given a normal hematocrit (branch point 4.4), this indicates a cardiovascular disorder with a low nonchanging O_2 pulse (branch point 4.6). The patient's limiting symptoms were typical of claudication due to peripheral arterial disease. Exercise-induced systemic hypertension (Table 10.21.3), low $\Delta\dot{V}O_2/\Delta WR$ and low $\Delta\dot{V}CO_2/\Delta WR$ (Fig. 10.21.1, panel 1), and high heart rate reserve are all consistent with peripheral arterial disease. The absence of ECG changes

Table 10.21.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		65
Sex		Male
Height (cm)		170
Weight (kg)	74	88
Hematocrit (%)		42
VC (L)	3.43	3.65
IC (L)	2.44	3.20
FEV_1 (L)	2.74	2.48
FEV_1/VC (%)	79	68
MVV (L/min)	110	92

Table 10.21.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.04	1.06
Maximum heart rate (beats/min)	155	135
Maximum O_2 pulse (mL/beat)	13.2	7.9
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	6.9
AT (L/min)	>0.95	0.8
Blood pressure (mm Hg [rest, max])		164/88, 278/110
Maximum $\dot{V}E$ (L/min)		33
Exercise breathing reserve (L/min)	>15	59
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.7	25.2

Table 10.21.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	164/88																		
0.5	Rest		95	22	12.8	0.36	0.36	3.8	1.00			106			38			30	30	
1.0	Rest	188/80	93	21	11.1	0.32	0.36	3.9	0.89			110			41			29	26	
1.5	Rest		95	19	11.2	0.32	0.35	3.7	0.91			108			38			30	27	
2.0	Rest	218/80	94	20	10.6	0.30	0.33	3.5	0.91			105			39			30	27	
2.5	Rest		97	22	8.0	0.20	0.23	2.4	0.87			105			40			31	27	
3.0	Rest	198/82	98	20	10.3	0.29	0.35	3.6	0.83			105			40			30	25	
3.5	Unloaded		110	20	14.1	0.46	0.52	4.7	0.88			104			41			27	24	
4.0	Unloaded	214/100	110	20	13.5	0.44	0.54	4.9	0.81			100			42			27	22	
4.5	Unloaded		113	20	13.4	0.39	0.49	4.3	0.80			108			37			30	24	
5.0	Unloaded	239/96	112	20	17.3	0.62	0.72	6.4	0.86			100			43			25	22	
5.5	Unloaded		113	19	17.8	0.63	0.72	6.4	0.88			101			44			26	22	
6.0	Unloaded	254/90	111	22	17.1	0.59	0.68	6.1	0.87			101			44			26	22	
6.5	7.5		115	20	19.2	0.69	0.75	6.5	0.92			102			44			25	23	
7.0	15	255/100	117	20	19.2	0.70	0.76	6.5	0.92			103			43			25	23	
7.5	22.5		119	22	20.6	0.74	0.79	6.6	0.94			103			43			25	24	
8.0	30	245/114	121	19	23.7	0.88	0.94	7.8	0.94			103			43			25	23	
8.5	37.5		122	21	23.7	0.88	0.91	7.5	0.97			103			44			25	24	
9.0	45	252/110	125	21	24.7	0.91	0.94	7.5	0.97			103			44			25	24	
9.5	52.5		127	19	24.8	0.92	0.92	7.2	1.00			105			44			25	25	
10.0	60	256/114	130	21	29.7	1.08	1.04	8.0	1.04			107			43			26	27	
10.5	67.5		131	21	32.7	1.15	1.07	8.2	1.07			109			42			27	29	
11.0	75	278/110	135	24	32.6	1.13	1.06	7.9	1.07			111			42			27	29	
11.5	Recovery		126	21	28.4	1.02	0.95	7.5	1.07			108			44			26	26	
12.0	Recovery	269/90	124	20	26.5	0.95	0.86	6.9	1.10			109			44			26	29	
12.5	Recovery		119	26	22.6	0.71	0.63	5.3	1.13			115			40			29	32	
13.0	Recovery	241/86	113	23	21.2	0.72	0.64	5.7	1.13			111			42			27	30	

indicative of myocardial ischemia, despite the exaggerated exercise blood pressure response, suggests that the coronary vessels are relatively uninvolved.

Conclusion

This patient has typical symptoms of peripheral arterial disease reflecting impaired oxygen supply to exercising muscle. Not surprisingly, this impairment is reflected in abnormalities of $\dot{V}O_2$. In addition, in contrast to other cardiovascular diseases, the increase in $\dot{V}CO_2$ relative to work rate was reduced as well, similar to the $\dot{V}O_2$–work rate relationship. This may be a reflection of diffuse lower extremity vascular disease constraining leg blood flow so severely that it constituted an abnormally low proportion of the total circulation perfusing the exercising muscles. Consequently, there was less CO_2 as well as less O_2 extracted in the venous return. Thus both $\dot{V}O_2$ and $\dot{V}CO_2$ were reduced as work rate was increased. This would be consistent with the patient's bilateral symptoms affecting both proximal and distal muscle groups. Although many patients with peripheral arterial disease are limited by associated coronary artery disease, this does not seem to be true for this man.

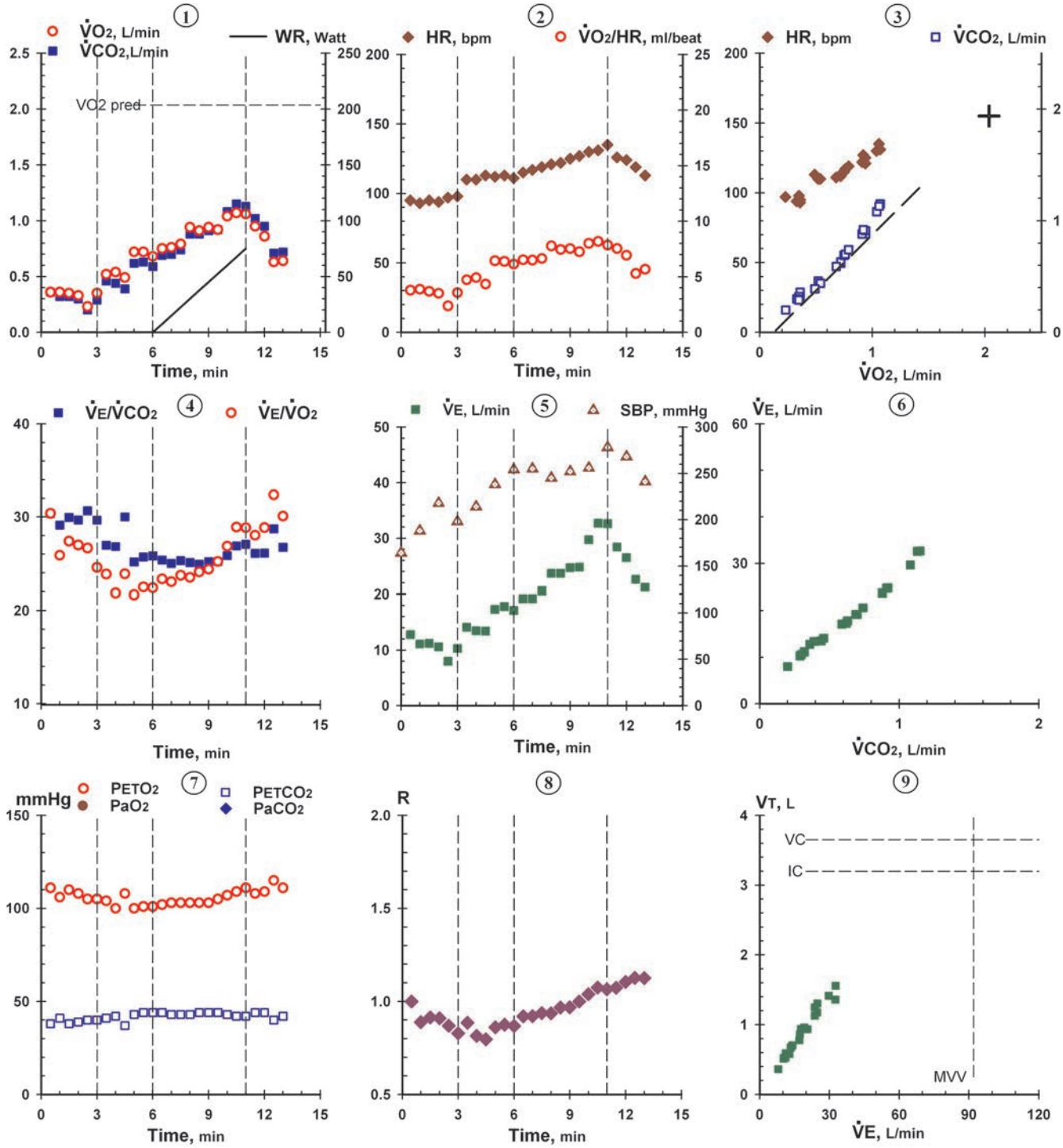

FIGURE 10.21.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 22 Cardiovascular Impairment with Hypertension and Carboxyhemoglobinemia

CLINICAL FINDINGS

A 46-year-old shipyard worker was referred for evaluation of shortness of breath. He complained of chronic cough and sputum production of 8 to 10 years' duration. He dated the shortness of breath to a hospitalization for a leg fracture 6 years before. He gave a history of cigarette smoking and heavy alcohol use. Physical examination revealed hepatomegaly without other evidence of liver disease. There were no physical signs of cardiovascular or pulmonary disease. Chest roentgenogram showed small bilateral pleural plaques. ECG showed a left anterior hemiblock.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 20 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. He stopped exercise complaining of shortness of breath and exhaustion. Carboxyhemoglobin level was 7.5% at the start of exercise, suggesting that the patient had recently smoked. There was no chest pain or abnormal ECG changes.

Table 10.22.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		46
Sex		Male
Height (cm)		161
Weight (kg)	67	70
Hematocrit (%)		43
VC (L)	3.32	3.23
IC (L)	2.22	2.24
TLC (L)	4.77	4.77
FEV_1 (L)	2.65	2.62
FEV_1/VC (%)	80	81
MVV (L/min)	122	104
DLCO (mL/mm Hg/min)	22.3	22.1

INTERPRETATION

Comments

Respiratory function at rest was normal (Table 10.22.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and anaerobic threshold were reduced (Table 10.22.2). Proceeding to Flowchart 4 (Fig. 8.4, branch point 4.1), the breathing reserve was high (Table 10.22.2). The ventilatory equivalent for CO_2 at the anaerobic threshold was normal (Fig. 10.22.1), and the indices of distribution of ventilation relative to perfusion were normal (branch point 4.3), supporting the diagnosis of an O_2 flow problem of nonpulmonary origin. The hematocrit

Table 10.22.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.26	1.17
Maximum heart rate (beats/min)	174	149
Maximum O_2 pulse (mL/beat)	13.0	8.1
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	7.6
AT (L/min)	>0.97	0.9
Blood pressure (mm Hg [rest, max])		168/108, 228/126
Maximum $\dot{V}E$ (L/min)		45
Exercise breathing reserve (L/min)	>15	59
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.0	31.9
PaO_2 (mm Hg [rest, max ex])		93, 101
$P(A-a)O_2$ (mm Hg [rest, max ex])		12, 21
$PaCO_2$ (mm Hg [rest, max ex])		35, 34
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		0, –2
VD/VT (rest, heavy ex)		0.25, 0.19
HCO_3^- (mEq/L [rest, 2-min recov])		23, 18

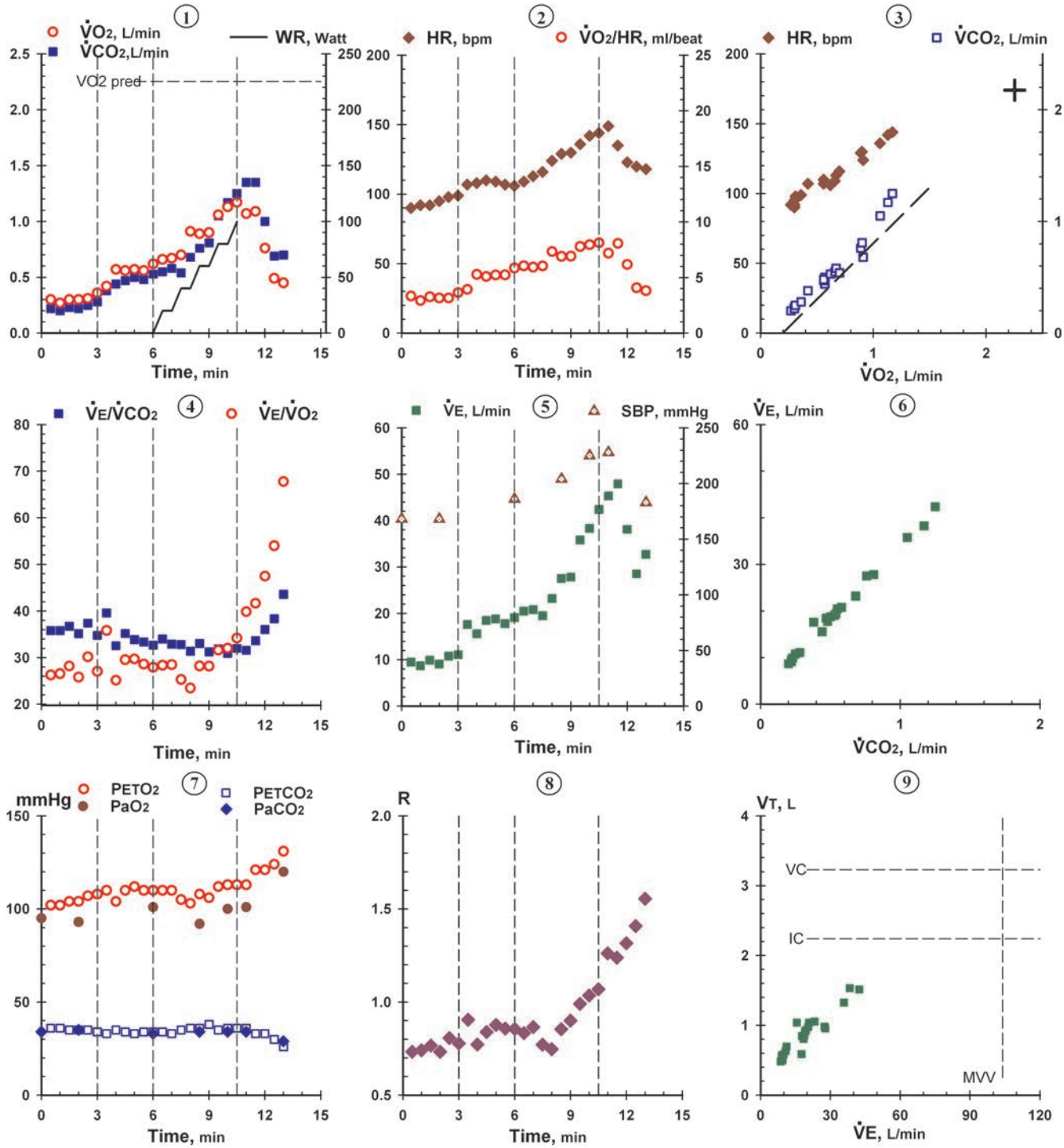

FIGURE 10.22.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.22.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
	Rest	168/108								7.44	23		95			34				
0.5	Rest		90	19	9.5	0.22	0.30	3.3	0.73			102			36			36	26	
1.0	Rest		92	18	8.7	0.20	0.27	2.9	0.74			102			36			36	27	
1.5	Rest		92	17	9.9	0.23	0.30	3.3	0.77			104			35			37	28	
2.0	Rest	168/108	95	16	9.1	0.22	0.30	3.2	0.73	7.41	22	104	93	12	35	35	0	35	26	0.25
2.5	Rest		98	17	10.8	0.25	0.31	3.2	0.81			107			35			37	30	
3.0	Rest		99	16	11.1	0.28	0.36	3.6	0.78			108			34			35	27	
3.5	Unloaded		107	30	17.6	0.38	0.42	3.9	0.90			110			33			40	36	
4.0	Unloaded		108	15	15.6	0.44	0.57	5.3	0.77			104			35			33	25	
4.5	Unloaded		110	23	18.5	0.47	0.56	5.1	0.84			110			34			35	30	
5.0	Unloaded		109	22	18.8	0.50	0.57	5.2	0.88			112			33			34	30	
5.5	Unloaded		107	21	17.8	0.48	0.56	5.2	0.86			110			34			33	29	
6.0	Unloaded	186/111	106	21	19.1	0.53	0.62	5.8	0.85	7.45	23	110	101	12	34	33	–1	33	28	0.18
6.5	20		109	21	20.5	0.55	0.66	6.1	0.83			110			34			34	28	
7.0	20		113	20	20.8	0.58	0.67	5.9	0.87			110			33			33	29	
7.5	40		116	21	19.5	0.54	0.70	6.0	0.77			105			35			33	25	
8.0	40		124	22	23.2	0.68	0.91	7.3	0.75			103			36			31	23	
8.5	60	204/120	129	28	27.5	0.76	0.89	6.9	0.85	7.43	22	108	92	19	36	34	–2	33	28	0.21
9.0	60		130	29	27.8	0.81	0.90	6.9	0.90			106			38			31	28	
9.5	80		136	27	35.8	1.05	1.06	7.8	0.99			112			35			32	32	
10.0	80	225/123	142	25	38.3	1.17	1.13	8.0	1.04	7.41	21	113	100	17	36	34	–2	31	32	0.17
10.5	100		144	28	42.4	1.25	1.17	8.1	1.07			113			36			32	34	
11.0	Recovery	228/126	149	31	45.3	1.35	1.07	7.2	1.26	7.40	21	113	101	21	36	34	–2	32	40	0.19
11.5	Recovery		135	29	47.9	1.35	1.09	8.1	1.24			121			33			34	42	
12.0	Recovery	269/90	123	24	38.1	1.00	0.76	6.2	1.32			121			33			36	47	
12.5	Recovery		120	24	28.5	0.69	0.49	4.1	1.41			124			30			38	54	
13.0	Recovery	183/111	118	26	32.7	0.70	0.45	3.8	1.56	7.41	18	131	120	9	26	29	3	44	68	0.30

was normal (branch point 4.4). The maximum O_2 pulse was reduced but increasing (branch point 4.6). Although the heart rate reserve was high, the early occurrence of the anaerobic threshold and shallow $\Delta\dot{V}O_2/\Delta WR$ indicate that this was not simply a matter of the subject performing a submaximal effort, but that there was some form of cardiovascular impairment. The high heart rate reserve and hypertensive response to exercise (Table 10.22.3) are consistent with peripheral arterial disease, although there were no specific findings to confirm this condition. Alternatively, exercise cardiac output might be impaired due to hypertensive heart disease or cardiomyopathy. Either of these, or other cardiovascular pathologies, would be consistent with the shallow $\Delta\dot{V}O_2/\Delta WR$. There was no chest pain or ECG abnormalities to specifically implicate coronary artery disease as the cause of impairment.

Conclusion

The patient evidently has exercise intolerance secondary to cardiovascular disease, although the exact site of dysfunction was not clear and follow-up studies are indicated. The reduced arterial O_2 content of the blood and leftward shift of the oxyhemoglobin dissociation curve, due to elevated carboxyhemoglobin concentration, contribute to the O_2 flow problem but are unlikely to fully account for the extent of impairment.

Case 23 Rate Disturbance due to β-Adrenergic Blockade for Treatment of Systemic Hypertension

CLINICAL FINDINGS

A 60-year-old woman was evaluated because of chronic cough and moderate exertional dyspnea. She had systemic arterial hypertension, for which she was treated with a β-adrenergic blocker and diuretic. An angiotensin-converting enzyme (ACE) inhibitor had not been prescribed because of the chronic cough. She had never smoked. Her resting ECG was normal. At her initial exercise evaluation, she had a reduced exercise tolerance, with a reduced heart rate response and poor control of her hypertension. To determine whether the limited heart rate accounted for exercise intolerance, she had repeat testing performed after holding her beta-blocker. Both tests are shown. The first (Fig. 10.23.1) was done while taking the beta-blocker, and the second (Fig. 10.23.2) 2 days later after the β-adrenergic blocker had been withheld.

EXERCISE FINDINGS

On both tests, the patient performed exercise on a cycle ergometer. She cycled at 60 rpm without added load for 3 minutes, after which work rate was progressively increased by 10 W per minute until she could not continue. Heart rate and rhythm were continuously monitored and arterial pressure was measured every 2 minutes by sphygmomanometer. The patient performed the tests with good effort and ended both with symptoms of leg fatigue.

Table 10.23.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		60
Sex		Female
Height (cm)		165
Weight (kg)		59
Hematocrit (%)		41
VC (L)	3.22	2.74
IC (L)	2.15	1.75
ERV (L)	1.07	1.00
FEV_1 (L)	2.53	1.76
FEV_1/VC (%)	78	64
MVV (L/min)	104	70
DLCO (mL/mm Hg/min)	25.2	11.1

INTERPRETATION

Comments

Resting pulmonary function showed moderate airway obstruction with significant reduction in her diffusing capacity (Table 10.23.1). Her maximum heart rate on exercise testing was 113 bpm with and 156 bpm without β-adrenergic blockade (Table 10.23.2). Exercise ECGs were otherwise unremarkable. Her blood pressure response was similar on the 2 days of testing (Tables 10.23.3 and 10.23.4).

Analysis

Referring to the first test (Table 10.23.2 and Fig. 10.23.1), the peak $\dot{V}O_2$ and *AT* were low, leading in Flowchart 1 (Fig. 8.1) through branch points 1.1, 1.2, and 1.3 to Flowchart 4 (Fig. 8.4). The breathing reserve was borderline normal (branch point 4.1), and the ventilatory equivalent for $\dot{V}CO_2$ at the *AT*

Table 10.23.2

Selected Exercise Data

Measurement	Predicted	With β-blockade	Without β-blockade
Peak $\dot{V}O_2$ (L/min)	1.31	1.07	1.22
Maximum heart rate (beats/min)	160	113	156
Maximum O_2 pulse (mL/beat)	8.2	9.5	7.8
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	6.8	8.7
AT (L/min)	>0.68	0.50	0.80
Blood pressure (mm Hg [rest, max])		180/85, 200/100	170/90, 220/100
Maximum $\dot{V}E$ (L/min)		54	55
Exercise breathing reserve (L/min)	>15	16	15
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	29.4	31.5	29.2
$PETCO_2$ at *AT*	>40	38	40
$\dot{V}E$ vs. $\dot{V}CO_2$	<32	29	27
SaO_2 (pulse oximeter, % [rest, exercise])	>95	97, 97	95, 95

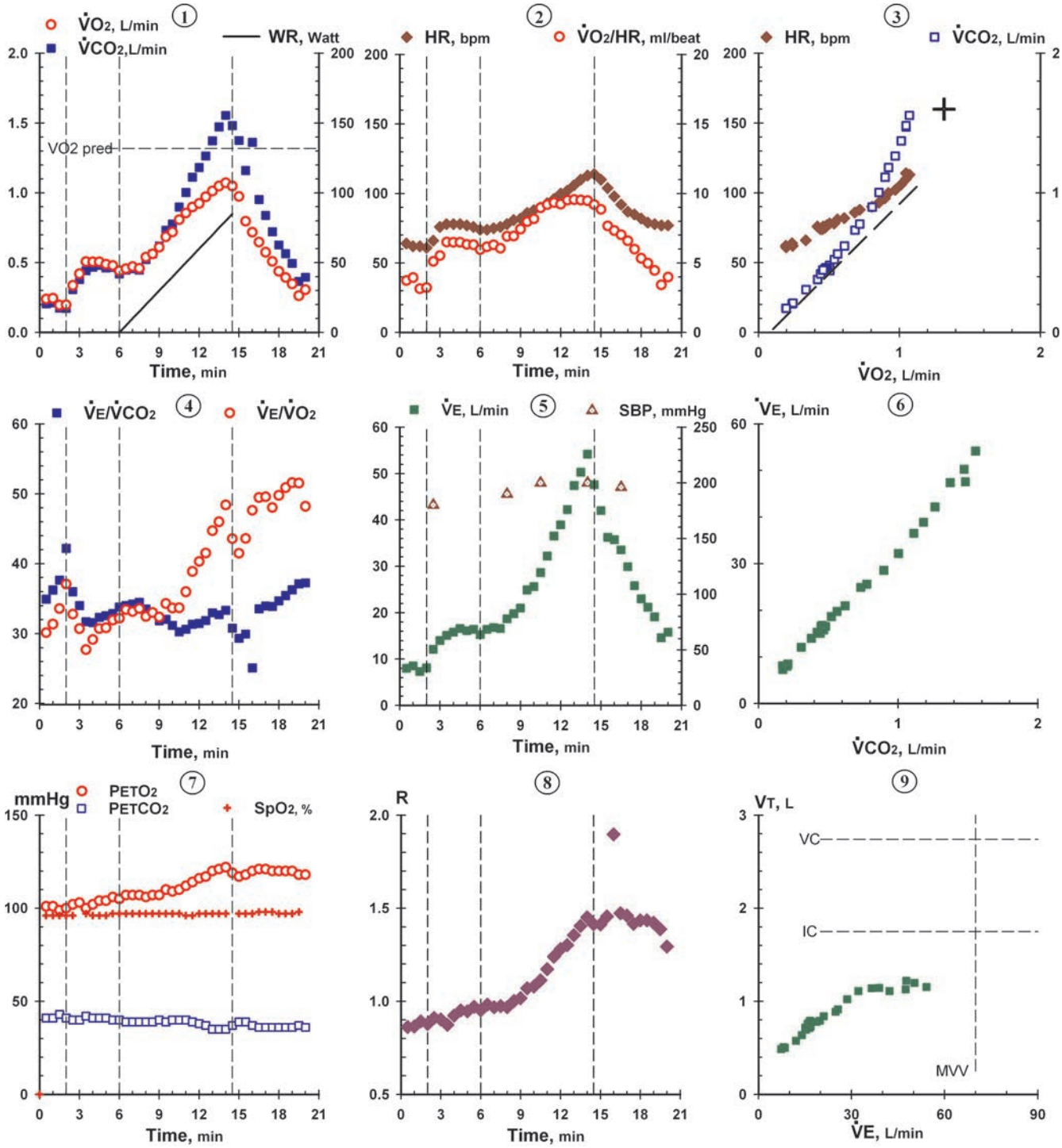

FIGURE 10.23.1. First study, while taking β-adrenergic blocker. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.23.3

On β-adrenergic Blockade Medication

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest		64	16	8.0	0.21	0.24	3.7	0.86			101			41			35	30	
1.0	Rest		62	17	8.5	0.21	0.24	3.9	0.86			101			41			36	31	
1.5	Rest		62	15	7.3	0.17	0.20	3.1	0.89			99			43			38	34	
2.0	Rest		61	16	8.1	0.17	0.20	3.2	0.88			100			41			42	37	
2.5	Rest	180/85	66	21	12.1	0.31	0.34	5.1	0.91			102			40			36	33	
3.0	Rest		76	22	14.0	0.38	0.42	5.5	0.90			103			40			34	31	
3.5	Unloaded		78	21	15.1	0.44	0.51	6.5	0.87			100			42			32	28	
4.0	Unloaded		78	21	15.8	0.47	0.51	6.5	0.92			102			41			32	29	
4.5	Unloaded		78	21	16.6	0.48	0.51	6.5	0.95			104			41			32	31	
5.0	Unloaded		77	21	16.1	0.46	0.49	6.3	0.95			104			41			33	31	
5.5	Unloaded		76	22	16.4	0.47	0.48	6.3	0.97			106			40			33	32	
6.0	Unloaded		74	22	15.3	0.42	0.44	6.0	0.95			105			40			34	32	
6.5	5		74	23	16.4	0.45	0.46	6.2	0.98			107			39			34	33	
7.0	10		75	23	16.8	0.46	0.47	6.3	0.97			107			39			34	33	
7.5	15		76	23	16.6	0.45	0.46	6.1	0.97			107			39			34	34	
8.0	20	190/90	78	24	18.7	0.52	0.54	6.9	0.97			106			39			34	32	
8.5	25		81	25	19.8	0.56	0.56	6.9	1.00			107			39			33	33	
9.0	30		82	25	21.0	0.62	0.61	7.4	1.02			107			40			32	32	
9.5	35		86	28	24.9	0.73	0.69	8.0	1.07			110			39			32	34	
10.0	40		88	28	25.6	0.78	0.72	8.2	1.08			109			40			31	34	
10.5	45	200/96	90	28	28.6	0.90	0.81	9.0	1.11			110			40			30	34	
11.0	50		93	29	32.2	1.00	0.86	9.2	1.17			112			40			31	36	
11.5	55		96	32	36.5	1.11	0.90	9.4	1.24			114			39			31	39	
12.0	60		100	34	38.9	1.18	0.92	9.2	1.28			116			38			31	40	
12.5	65		102	38	42.2	1.26	0.97	9.5	1.30			117			37			32	42	
13.0	70		106	42	47.4	1.37	1.01	9.6	1.36			120			35			33	45	
13.5	75		110	42	50.3	1.47	1.05	9.5	1.41			121			35			33	46	
14.0	80	200/100	113	47	54.2	1.56	1.07	9.5	1.45			122			35			33	48	
14.5	85		114	39	47.6	1.48	1.05	9.2	1.41			119			37			31	44	
15.0	90		110	33	42.0	1.38	0.97	8.8	1.41			117			39			29	41	
15.5	Recovery		104	29	36.2	1.16	0.80	7.7	1.46			118			39			30	44	
16.0	Recovery		98	30	35.7	1.36	0.72	7.3	1.90			120			37			25	48	
16.5	Recovery	196/90	92	30	33.5	0.95	0.65	7.0	1.47			121			36			34	49	
17.0	Recovery		87	29	29.9	0.84	0.57	6.6	1.46			121			36			34	50	
17.5	Recovery		85	27	25.8	0.72	0.51	6.0	1.42			120			36			34	48	
18.0	Recovery		82	25	23.0	0.63	0.44	5.3	1.43			120			36			35	50	
18.5	Recovery		79	24	21.2	0.56	0.39	5.0	1.44			120			36			35	51	
19.0	Recovery		78	23	19.1	0.50	0.35	4.5	1.42			120			36			36	52	
19.5	Recovery		77	21	14.6	0.37	0.26	3.4	1.39			118			37			37	52	
20.0	Recovery		77	21	15.8	0.40	0.31	4.0	1.29			118			36			37	48	

(branch point 4.3) was normal, leading to the category of O_2 flow problem of nonpulmonary origin (anemia, heart disease, or peripheral arterial disease). She was not anemic (Table 10.23.1). Her ECG was normal during this test and she had no symptoms of claudication. The increase in $\dot{V}O_2$ as related to work rate was normal at low work rates but became more shallow as peak $\dot{V}O_2$ was approached, making the calculated $\Delta\dot{V}O_2/\Delta WR$ slope low (panel 3, Fig. 10.23.1 and Table 10.23.2).

Two days later, after withholding her β-adrenergic blocker, the peak $\dot{V}O_2$ and anaerobic threshold were normal. The $\Delta\dot{V}O_2/\Delta WR$ was also normalized. With these variables as well as the peak O_2 pulse, $\dot{V}E/\dot{V}CO_2$, $PETCO_2$ at the anaerobic threshold, and ECG all being normal, there are no findings to suggest cardiac or pulmonary vascular disease. She had inadequately controlled hypertension on both tests, but this did not appear to limit exercise tolerance as much as the drug that she was taking to treat it. Studies performed at rest suggested lung disease as the cause of her symptoms. Although the cause of her lung disease remained to be determined, it did not appear to be the proximal cause of her exercise limitation.

Conclusion

The patient was on a drug regimen that reduced her exercise tolerance without effectively controlling her hypertension. This case illustrates that cardiopulmonary exercise testing may help in the selection and dose titration of cardiovascular medications.

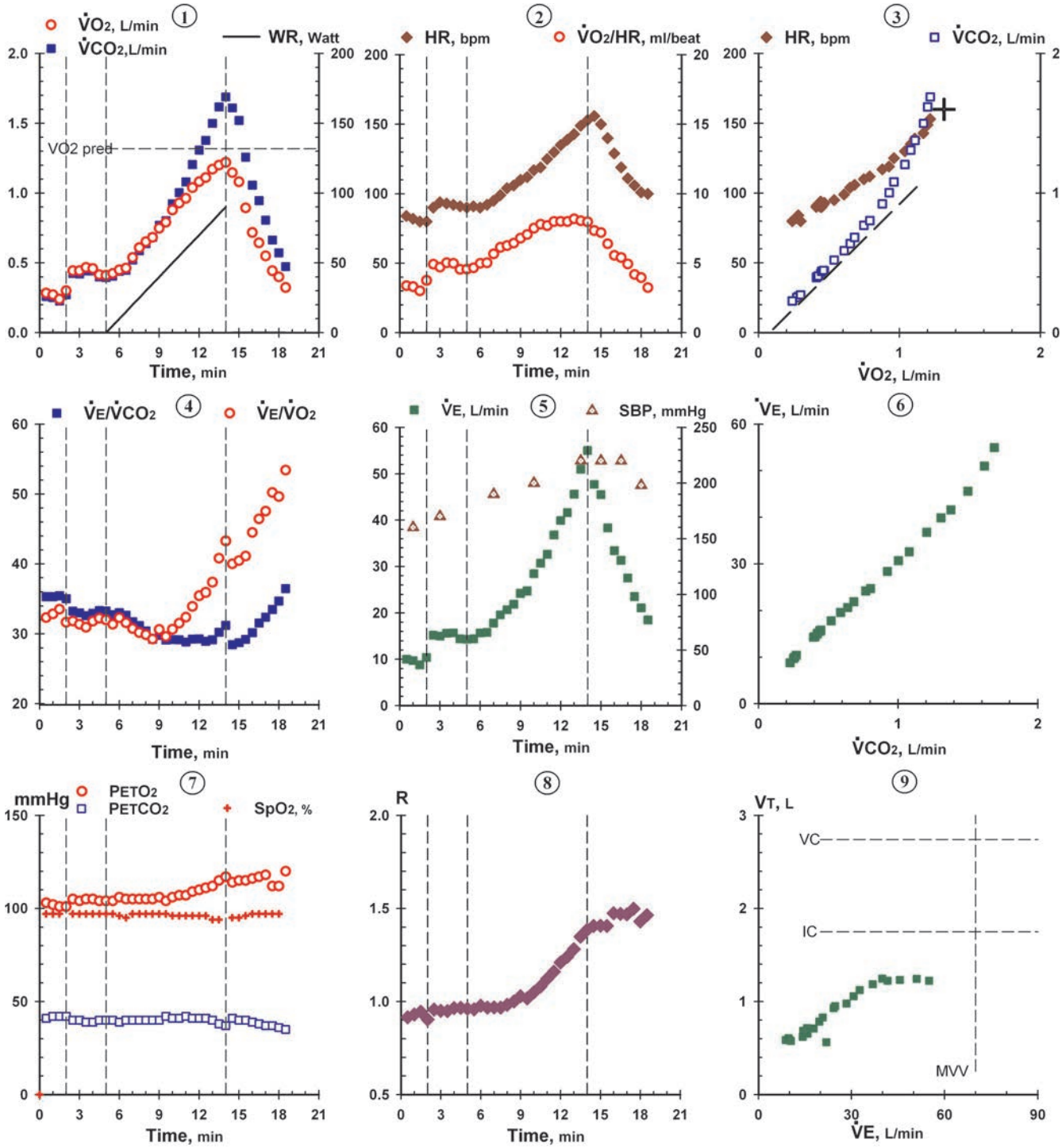

FIGURE 10.23.2. Second study, without β-adrenergic blocker. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.23.4

Off β-adrenergic Blockade Medication

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest		84	17	10.0	0.26	0.28	3.4	0.92			103			41			35	32	
1.0	Rest	160/80	82	16	9.7	0.25	0.27	3.3	0.93			102			42			35	33	
1.5	Rest		80	15	8.8	0.23	0.24	3.0	0.95			101			42			35	34	
2.0	Rest		80	18	10.4	0.27	0.30	3.8	0.90			101			42			35	32	
2.5	Unloaded		90	22	15.2	0.42	0.44	4.9	0.96			105			40			33	32	
3.0	Unloaded	170/90	94	22	15.0	0.42	0.44	4.7	0.95			104			40			33	31	
3.5	Unloaded		93	23	15.6	0.44	0.47	5.0	0.95			105			39			33	31	
4.0	Unloaded		92	22	15.7	0.44	0.46	5.0	0.97			105			39			33	32	
4.5	Unloaded		91	21	14.4	0.40	0.41	4.5	0.97			104			40			33	32	
5.0	Unloaded		90	23	14.3	0.40	0.41	4.6	0.96			104			40			33	32	
5.5	5		91	22	14.4	0.41	0.42	4.7	0.96			104			40			33	31	
6.0	10		90	24	15.7	0.44	0.45	5.0	0.98			106			39			33	32	
6.5	15		92	24	15.8	0.45	0.46	5.0	0.97			105			40			33	32	
7.0	20	190/90	95	25	17.8	0.52	0.54	5.7	0.97			105			40			32	31	
7.5	25		99	25	19.6	0.59	0.61	6.1	0.97			105			40			31	30	
8.0	30		104	25	20.7	0.64	0.65	6.3	0.98			105			40			30	30	
8.5	35		106	39	21.9	0.68	0.68	6.4	1.00			105			40			29	29	
9.0	40		110	26	24.2	0.77	0.75	6.8	1.03			106			40			30	31	
9.5	45		112	26	24.7	0.80	0.79	7.1	1.02			104			42			29	30	
10.0	50	200/100	117	29	28.4	0.92	0.88	7.5	1.05			106			41			29	31	
10.5	55		119	29	30.7	1.00	0.93	7.8	1.08			107			41			29	32	
11.0	60		125	29	32.6	1.08	0.96	7.7	1.12			107			42			29	32	
11.5	65		130	31	36.8	1.21	1.04	8.0	1.16			109			41			29	34	
12.0	70		135	32	39.9	1.31	1.08	8.0	1.21			110			41			29	35	
12.5	75		139	34	41.6	1.38	1.11	8.0	1.24			111			41			29	36	
13.0	80		143	37	45.6	1.50	1.17	8.2	1.28			112			40			29	37	
13.5	85	220/100	149	41	51.0	1.62	1.20	8.1	1.35			115			38			30	41	
14.0	90		153	45	55.0	1.69	1.22	8.0	1.39			117			37			31	43	
14.5	Recovery		156	37	47.7	1.61	1.15	7.3	1.41			114			41			28	40	
15.0	Recovery	220/100	150	36	45.5	1.52	1.08	7.2	1.41			115			40			29	40	
15.5	Recovery		140	31	38.3	1.26	0.89	6.4	1.41			115			40			29	41	
16.0	Recovery		129	30	33.4	1.06	0.72	5.6	1.47			116			39			30	44	
16.5	Recovery	220/100	119	29	31.3	0.95	0.64	5.4	1.47			117			38			32	46	
17.0	Recovery		111	28	27.5	0.81	0.55	4.9	1.47			118			37			32	48	
17.5	Recovery		106	25	23.5	0.66	0.44	4.2	1.50			112			37			34	50	
18.0	Recovery	198/90	101	25	21.1	0.57	0.40	4.0	1.43			112			36			35	50	
18.5	Recovery		100	25	18.5	0.47	0.32	3.2	1.46			120			35			36	53	

Case 24 Atrial Fibrillation with Rapid Ventricular Response during Exercise

CLINICAL FINDINGS

A 70-year-old woman was referred for exercise testing to evaluate a finding of pulmonary hypertension on echocardiogram. The study had also demonstrated mitral and tricuspid regurgitation but normal right and left ventricular size and function. Both a sleep study and a computed tomography pulmonary angiogram had been reported as normal. She did not complain of exertional dyspnea during her normal activities, but she had a largely sedentary lifestyle and seldom did more than walk within her home and office. She did note that she was short of breath if walking up an incline. She had a history of systemic hypertension, hyperlipidemia, and chronic atrial fibrillation. Her medications included warfarin, atenolol, amlodipine, clonidine, simvastatin, and hydrochlorothiazide. Examination was notable for a holosystolic murmur at the cardiac apex. Lungs were clear to auscultation and there was no peripheral edema. The resting ECG showed atrial fibrillation with a ventricular rate ranging from 80 to 90.

EXERCISE FINDINGS

The patient exercised on a cycle ergometer. After 3 minutes of unloaded pedaling at 60 rpm, the work rate was increased progressively at a rate of 10 W per minute until she stopped with the primary symptom of leg fatigue. During the initial phase of unloaded cycling, heart rate increased rapidly to about 150 bpm. As work rate was increased, there was further increase of heart rate to 170 to 180 bpm, which was well above the patient's predicted maximal heart rate. There were no ischemic changes noted.

Table 10.24.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		70
Sex		Female
Height (cm)		157
Weight (kg)		79
VC (L)	2.76	2.25
IC (L)	2.05	2.01
FEV_1 (L)	2.08	1.97
FEV_1/VC (%)	76	88
MVV (L/min)	82	87
D_{LCO} (mL/mm Hg/min)	18.7	17.22

INTERPRETATION

Comments

Spirometry was normal (Table 10.24.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1 and Table 10.24.2), peak $\dot{V}O_2$ and the anaerobic threshold were both low (branch points 1.1, 1.2, and 1.3). Referring to Flowchart 4 (Fig. 8.4) the breathing reserve (branch point 4.1) was high while the $\dot{V}E/\dot{V}CO_2$ was also high. According to branch point 4.5, these findings, along with a normal pulse oximetry, suggest moderate-to-severe left ventricular heart failure, but this is unlikely given the normal echocardiogram at rest. Although the heart rate was irregular due to the arrhythmia, the pattern of increase in heart rate relative to $\dot{V}O_2$ (panel 3, Fig. 10.24.1) was clearly steep, with much of the increase in rate occurring during the unloaded cycling phase (panel 2, Fig. 10.24.1 and Table 10.24.3). The O_2 pulse was therefore low. Although a low O_2 pulse

Table 10.24.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.22	0.82
Maximum heart rate (beats/min)	150	185
Maximum O_2 pulse (mL/beat)	8.1	4.9
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	5.3
AT (L/min)	>0.68	0.58
Blood pressure (mm Hg [rest, max])		157/92, 202/115
Maximum $\dot{V}E$ (L/min)		39
Exercise breathing reserve (L/min)	>15	48
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	30.8	39.2

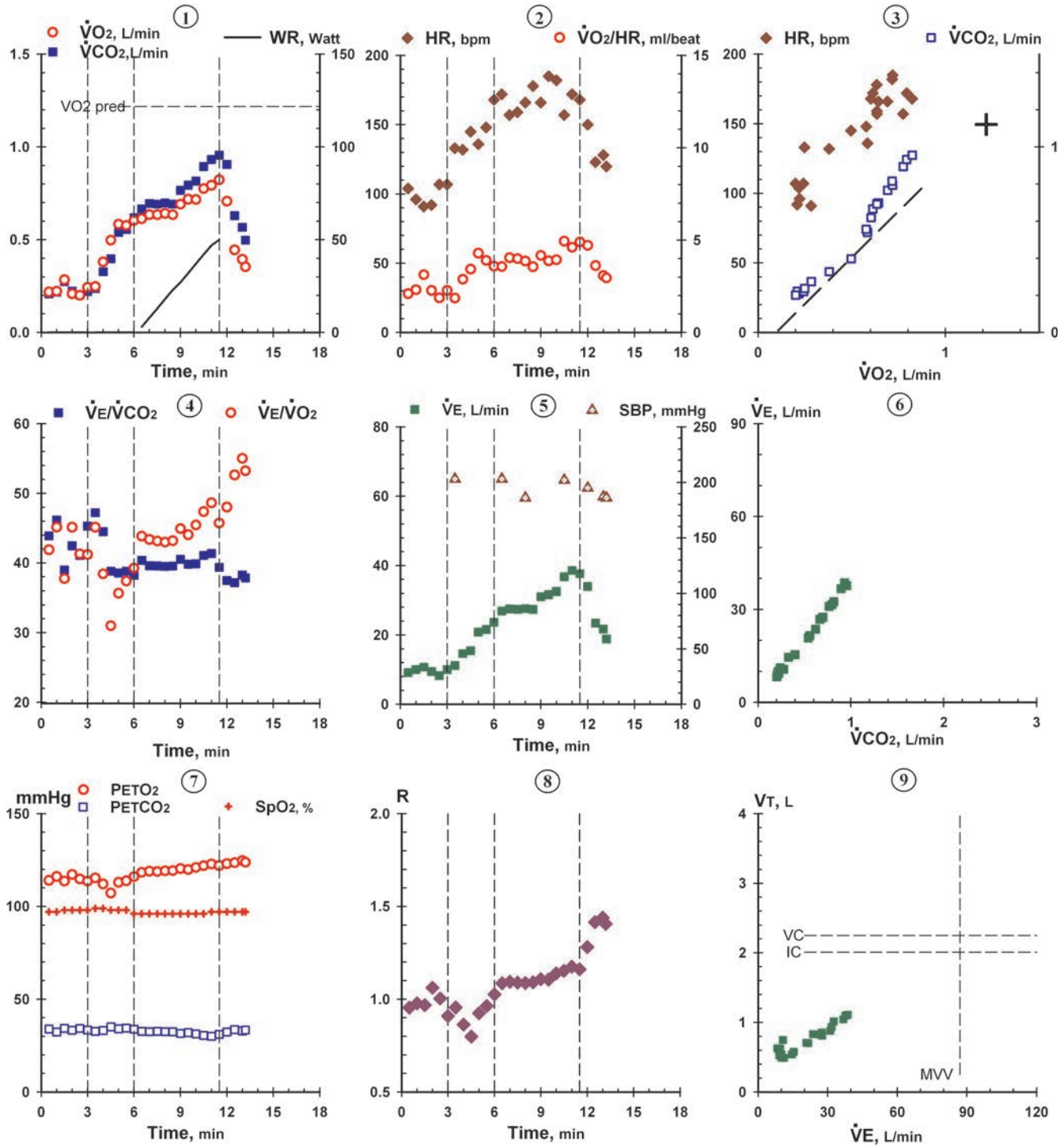

FIGURE 10.24.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.24.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest		104	17	9.1	0.21	0.22	2.1	0.95			114			34			44	42	
1.0	Rest		96	20	10.0	0.22	0.22	2.3	0.98			116			32			46	45	
1.5	Rest		91	14	10.7	0.28	0.28	3.1	0.97			114			34			39	38	
2.0	Rest		92	15	9.4	0.22	0.21	2.3	1.06			117			33			42	45	
2.5	Rest	157/92	107	13	8.3	0.20	0.20	1.9	1.01			115			34			41	41	
3.0	Rest		107	19	10.0	0.22	0.24	2.3	0.91			114			33			45	41	
3.5	Unloaded		133	23	11.2	0.24	0.25	1.9	0.96			115			33			47	45	
4.0	Unloaded		132	27	14.6	0.33	0.38	2.9	0.86			112			33			45	38	
4.5	Unloaded		145	27	15.4	0.40	0.50	3.4	0.80			107			35			39	31	
5.0	Unloaded		136	30	20.8	0.54	0.58	4.3	0.92			113			34			39	36	
5.5	Unloaded		148	31	21.6	0.56	0.58	3.9	0.96			114			34			39	37	
6.0	Unloaded		168	29	23.7	0.62	0.60	3.6	1.03			116			34			38	39	
6.5	3	203/113	172	32	26.9	0.67	0.61	3.6	1.09			118			33			40	44	
7.0	8		157	32	27.5	0.70	0.64	4.0	1.09			119			33			40	43	
7.5	13		159	33	27.4	0.69	0.64	4.0	1.09			119			33			40	43	
8.0	18	186/130	166	34	27.6	0.70	0.64	3.9	1.09			119			33			40	43	
8.5	23		178	33	27.4	0.69	0.63	3.6	1.09			119			32			40	43	
9.0	27		166	35	31.0	0.77	0.69	4.2	1.11			120			32			41	45	
9.5	32		185	34	31.6	0.79	0.72	3.9	1.11			120			32			40	44	
10.0	37		182	32	32.5	0.82	0.72	3.9	1.14			121			31			40	45	
10.5	42	202/115	157	35	36.7	0.89	0.78	4.9	1.15			122			31			41	47	
11.0	47		172	35	38.6	0.93	0.79	4.6	1.18			123			30			41	49	
11.5	50		168	34	37.6	0.96	0.82	4.9	1.16			122			31			39	46	
12.0	Recovery	195/157	150	31	34.0	0.91	0.71	4.7	1.28			123			32			37	48	
12.5	Recovery		123	23	23.4	0.63	0.45	3.6	1.42			124			34			37	53	
13.0	Recovery	187/140	128	24	21.7	0.57	0.39	3.1	1.44			125			33			38	55	
14.0	Recovery	186/138	120	21	18.8	0.50	0.35	3.0	1.41			124			33			38	53	

commonly reflects compensatory increase in heart rate in response to a reduced stroke volume, in the setting of atrial fibrillation with a rapid ventricular response, the low O_2 pulse, and presumably stroke volume, may be secondary to the fast rate, rather than the other way around. The low slope of $\dot{V}O_2$ relative to work rate and the early occurrence of the anaerobic threshold indicate that O_2 flow was not normal. Considering the ventilatory response to exercise, the ventilatory equivalents are mildly increased relative to predicted. This suggests abnormal pulmonary $\dot{V}A/\dot{Q}$ matching, which can occur as a consequence of a number of different conditions. Although idiopathic pulmonary arterial hypertension is characterized by high ventilatory equivalents, conditions causing pulmonary venous hypertension, such as chronic left ventricular failure, can also manifest this finding. In this case, the patient's mitral regurgitation and atrial fibrillation with poorly controlled ventricular rate could be causing pulmonary venous and, subsequently, pulmonary arterial hypertension.

Conclusion

This test is presented to illustrate the finding of excessive A-V conduction and reduced stroke volume during exercise associated with rapid atrial fibrillation. Even though ventricular heart rate appeared reasonably well-controlled at rest, it markedly accelerated during exercise, causing gas exchange abnormalities consistent with left ventricular failure.

Case 25 Chronotropic Insufficiency with Escape Rhythm

A 77-year-old man was referred for exercise testing for evaluation of unexplained dyspnea. He had mild-to-moderate aortic regurgitation and was being treated for systemic hypertension. He had been quite physically active, bicycling and running several times per week in the past, but noted progressive exertional dyspnea for 2 years, to the point that he was short of breath with brisk walking. He had no orthopnea, chest pain, or syncope. His medications included verapamil, statin, and furosemide. Examination revealed a soft decrescendo diastolic murmur and clear lung fields with no peripheral edema. The ECG showed a normal sinus rhythm, rate of 60, with an intraventricular conduction delay and occasional premature atrial contractions.

EXERCISE FINDINGS

Exercise testing was done on a cycle ergometer. After 3 minutes of unloaded pedaling at 60 rpm, the work rate was increased continuously by 15 W per minute until the patient stopped exercise due to shortness of breath. Over the first 7 minutes of exercise, heart rate increased only minimally, from 60 to 70 bpm. The rate then accelerated rapidly to 90 bpm (Fig. 10.25.1) associated with preserved QRS configuration but loss of P waves on the ECG, indicating an accelerated junctional rhythm. This rhythm persisted through the remainder of exercise with a peak heart rate of 93 bpm. Aside from the change in rhythm, there were no ischemic ECG changes, and the patient denied chest pain. The blood pressure response to exercise was normal. At just under 2 minutes of recovery, the cardiac rhythm reverted to sinus rhythm at a rate of 70 bpm.

Table 10.25.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		77
Sex		Male
Height (cm)		177
Weight (kg)		81
VC (L)	4.07	3.96
IC (L)	3.21	3.60
FEV_1 (L)	2.92	3.07
FEV_1/VC (%)	72	78
MVV (L/min)	117	94

INTERPRETATION

Comments

Spirometry was normal (Table 10.25.1).

Analysis

The obvious findings on this study were abnormal cardiac rate and rhythm during exercise. Following Flowchart 1 (Fig. 8.1) the low peak $\dot{V}O_2$ and low-normal *AT* (Table 10.25.2) would lead to Flowchart 3 (Fig. 8.3) with a primary differential diagnosis of limitation due to lung disease, coronary disease, or poor effort. In Flowchart 3 (Fig. 8.3), the normal breathing reserve prompts an assessment of the ECG for evidence of ischemia. ECG was not typical of ischemia, but rate and rhythm were abnormal. Although bradyarrhythmias may indicate ischemia, in this case, the absence of chest pain or ST-segment changes favor an intrinsic cardiac conduction disorder. The increase in heart rate relative to $\dot{V}O_2$ was shallow from the start of exercise (Fig. 10.25.1, panel 3) and, because the patient was not on a beta-blocker, suggests sinus node dysfunction. The emergence of a junctional rhythm during exercise in this situation is relatively uncommon. Because peak heart rate was reduced more than the peak $\dot{V}O_2$, the end-exercise O_2 pulse was high, reflecting a compensatory increase in stroke volume by the Starling mechanism despite the absence of the contribution of atrial contraction to forward flow. This also argues against the presence

Table 10.25.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.72	1.30
Maximum heart rate (beats/min)	143	94
Maximum O_2 pulse (mL/beat)	12.0	14.2
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	7.2
AT (L/min)	>0.82	0.84
Blood pressure (mm Hg [rest, max])		131/66, 188/81
Maximum $\dot{V}E$ (L/min)		63
Exercise breathing reserve (L/min)	>15	31
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	29.8	39.0

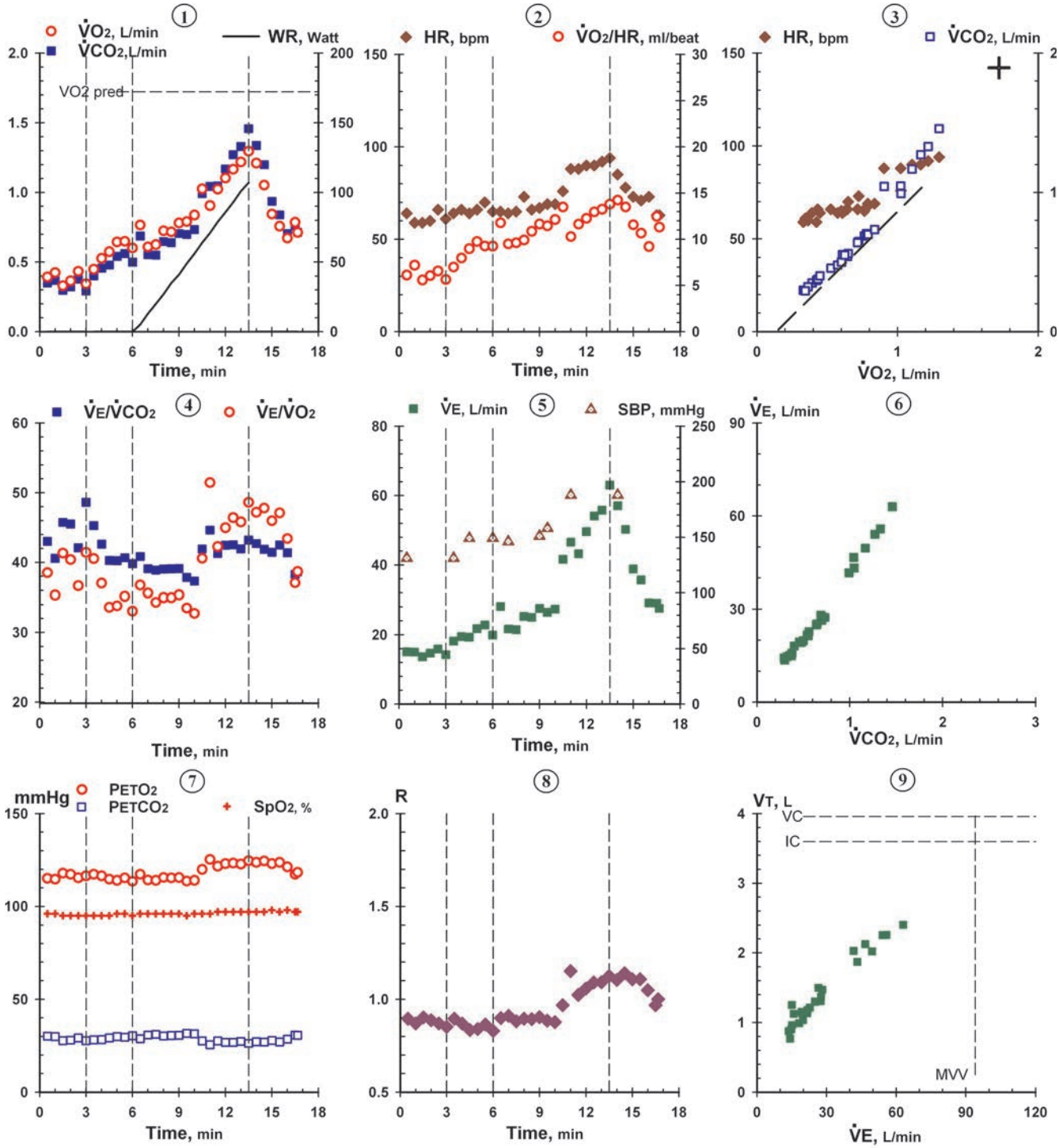

FIGURE 10.25.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 15 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $P_{ET}CO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

of myocardial ischemia. A surprising finding in this study was the striking changes in ventilation associated with the change in cardiac rhythm. Coincident with the loss of P waves, $\dot{V}E$ increased abruptly with corresponding increases in R, ventilatory equivalents, and end-tidal P_{O_2}, and decrease in end-tidal P_{CO_2} (Fig. 10.25.1 and Table 10.25.3), indicative of acute hyperventilation. Although this can result from a number of processes (e.g., acute onset of right-to-left shunting or idiopathic hyperventilation) in this case, the stability of pulse oximetry and breathing pattern, together with the ECG findings, suggest that it was a consequence of the change in rhythm. We speculate that the abrupt loss of coordinated atrial contractions resulted in increased stretch or pressure in the atria, which stimulated ventilation.

Conclusion

This test demonstrated exercise limitation due to chronotropic insufficiency. The sinus rate reached only about 70 bpm; a marginally higher rate was achieved by an accelerated junctional rhythm later in exercise. The gas exchange findings add to the assessment by demonstrating well-preserved inotropic function (high O_2 pulse), and also underscore the relationship between central hemodynamics and ventilatory drive.

Table 10.25.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{VD}{VT}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	131/66	64	16	15.1	0.35	0.39	6.1	0.90			115			30			43	39	
1.0	Rest		59	12	15.0	0.37	0.42	7.2	0.87			115			30			41	35	
1.5	Rest		59	16	13.6	0.30	0.33	5.6	0.90			118			28			46	41	
2.0	Rest		60	16	14.7	0.32	0.36	6.1	0.89			117			28			46	40	
2.5	Rest		66	14	15.9	0.38	0.43	6.6	0.87			115			29			42	37	
3.0	Rest		61	19	14.3	0.29	0.34	5.6	0.85			116			28			49	41	
3.5	Unloaded	131/66	64	18	18.2	0.40	0.45	7.0	0.90			117			28			45	41	
4.0	Unloaded		66	17	19.5	0.46	0.53	8.0	0.87			116			28			43	37	
4.5	Unloaded		64	17	19.3	0.48	0.57	9.0	0.83			115			29			40	34	
5.0	Unloaded	149/65	66	18	21.8	0.54	0.64	9.8	0.84			114			30			40	34	
5.5	Unloaded		70	19	22.8	0.56	0.65	9.3	0.86			115			30			41	35	
6.0	Unloaded		65	19	19.9	0.50	0.60	9.2	0.83			114			30			40	33	
6.5	5	149/65	65	19	28.1	0.69	0.77	11.8	0.90			117			29			41	37	
7.0	13		64	19	21.7	0.55	0.61	9.5	0.91			114			31			39	36	
7.5	20	146/81	65	19	21.4	0.55	0.63	9.6	0.88			114			31			39	34	
8.0	27		73	20	25.3	0.65	0.72	9.9	0.90			116			30			39	35	
8.5	35		66	19	25.0	0.64	0.72	10.8	0.89			115			31			39	35	
9.0	41		67	20	27.6	0.71	0.78	11.6	0.90			116			31			39	35	
9.5	49	158/73	69	18	26.5	0.70	0.79	11.4	0.88			114			32			38	33	
10.0	56		69	21	27.4	0.73	0.84	12.1	0.88			114			31			37	33	
10.5	64		76	21	41.6	0.99	1.03	13.5	0.97			120			28			42	41	
11.0	71		88	22	46.6	1.04	0.91	10.3	1.15			125			26			45	51	
11.5	79	188/69	88	23	43.2	1.05	1.02	11.6	1.02			122			28			41	42	
12.0	86		90	25	49.6	1.17	1.10	12.3	1.06			123			27			42	45	
12.5	93		90	24	54.1	1.27	1.17	13.0	1.09			123			27			43	46	
13.0	101		92	25	55.8	1.33	1.22	13.2	1.09			123			27			42	46	
13.5	107		94	26	63.0	1.46	1.30	13.8	1.13			125			26			43	49	
14.0	Recovery	188/69	85	30	57.1	1.34	1.21	14.2	1.10			124			27			43	47	
14.5	Recovery		78	25	50.3	1.20	1.05	13.5	1.14			125			27			42	48	
15.0	Recovery		73	22	38.8	0.94	0.84	11.6	1.11			123			28			41	46	
15.5	Recovery		71	21	35.7	0.84	0.76	10.7	1.11			124			27			42	47	
16.0	Recovery		73	20	29.2	0.71	0.67	9.2	1.05			121			29			41	43	
16.5	Recovery		63	20	29.1	0.76	0.79	12.5	0.97			117			31			38	37	

Case 26 Hypertrophic Cardiomyopathy with Postexercise Vasodepressor Syncope

CLINICAL FINDINGS

This 32-year-old man was seen by a cardiologist after his second episode of postexertional syncope, which occurred while playing basketball. Hypertrophic cardiomyopathy (HCM) was diagnosed based on echocardiogram findings that included moderate-to-severe concentric left ventricular hypertrophy with evidence of cavity obliteration and outflow track pressure gradient during exercise. He was advised that he was at risk for sudden death and should have an automatic defibrillator device implanted. He was hesitant to do so and sought the opinion of a second cardiologist who referred him for cardiopulmonary exercise testing as part of his evaluation. The patient had been active in vigorous athletics all of his life, playing tennis and team sports. There was no family history of heart disease or sudden death. He denied any chronic medical problems. He had been prescribed a β-adrenergic blocker but was not taking this or any medication. On exam, he appeared fit and had normal breath sounds and a midsystolic murmur. The ECG showed a sinus bradycardia and high QRS voltages with deep T-wave inversions consistent with left ventricular hypertrophy. Resting pulmonary function tests were normal (Table 10.26.1).

EXERCISE FINDINGS

Exercise testing was conducted on a cycle ergometer. After pedaling at 60 rpm for 3 minutes without added load, work rate was continuously increased by 30 W per minute until he stopped due to symptoms of tightness in the thighs. In the recovery period while the patient pedaled without resistance, he became lightheaded as his heart rate dropped abruptly from the peak value of 165 bpm to 30 to 40 bpm with occasional ventricular ectopy. As he was being assisted from the cycle and placed supine, the ECG recorded several asystolic pauses lasting 3 to 9 seconds each. He became transiently unresponsive but regained alertness as his heart rate and blood pressure recovered spontaneously. He felt back to his normal state within 5 minutes of ending exercise and the ECG, blood pressure, and clinical exam all returned to baseline within 15 minutes.

Analysis

Ventilatory gas exchange responses during exercise were all within normal ranges (Fig. 10.26.1). In particular, peak $\dot{V}O_2$ and anaerobic threshold were normal (Table 10.26.2).

Table 10.26.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		32
Sex		Male
Height (cm)		183
Weight (kg)		79
VC (L)	5.70	5.30
IC (L)	3.80	3.96
TLC (L)	7.54	6.73
FEV_1 (L)	4.71	4.43
FEV_1/VC (%)	83	84
MVV (L/min)	182	185
DLCO (mL/mm Hg/min)	35.7	27.0

Table 10.26.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	3.17	2.92
Maximum heart rate (beats/min)	188	166
Maximum O_2 pulse (mL/beat)	16.8	18.2
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	9.8
AT (L/min)	>1.37	1.50
Blood pressure (mm Hg [rest, max])		139/82, 199/124
Maximum $\dot{V}E$ (L/min)		97
Exercise breathing reserve (L/min)	>15	88
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	24.8	24.1

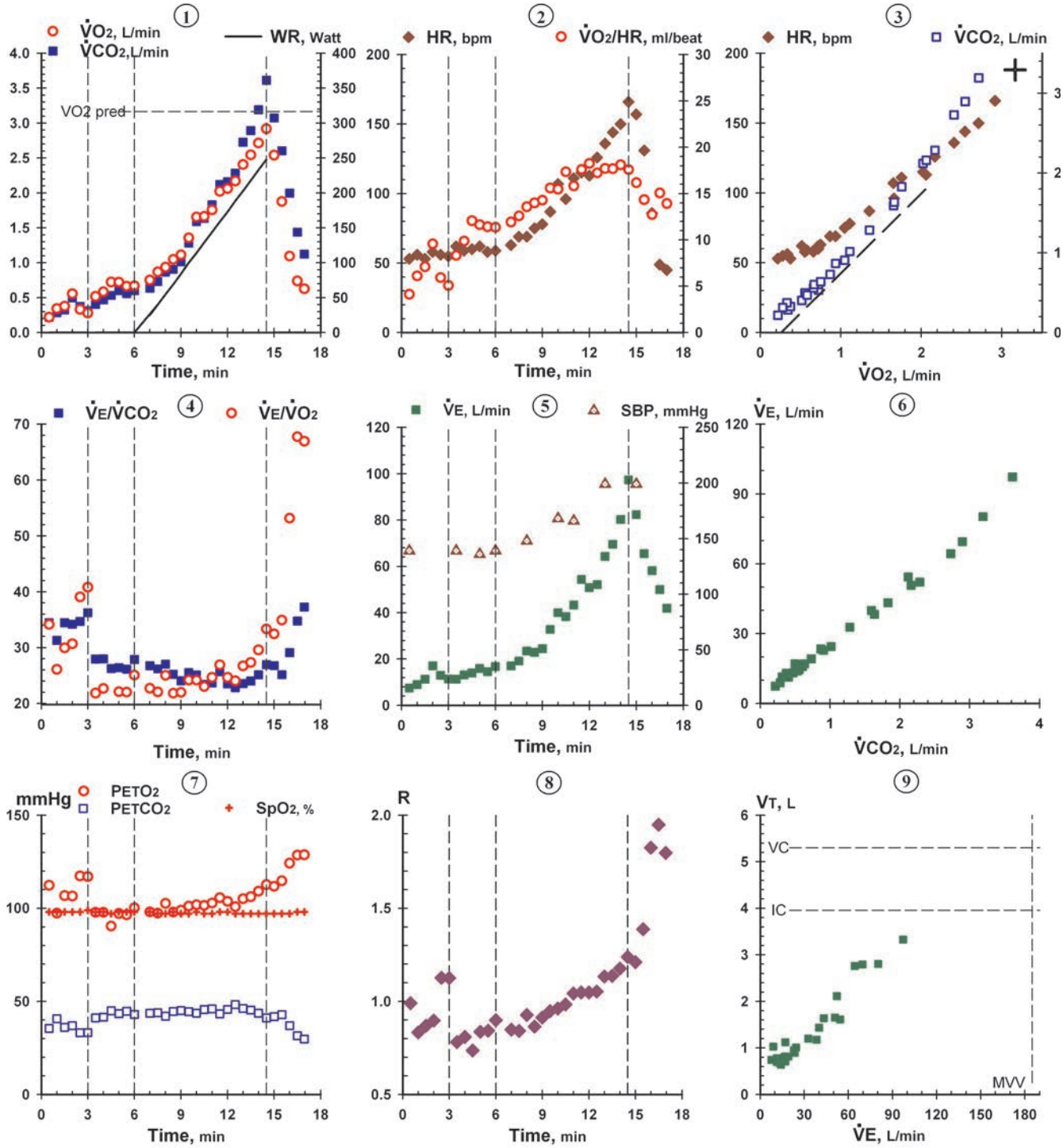

FIGURE 10.26.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 30 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $P_{ET}CO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.26.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0																				
0.5	Rest	139/82	53	10	7.5	0.22	0.22	4.1	0.99			112			36			34	34	
1.0	Rest		56	9	8.9	0.29	0.34	6.1	0.83			97			41			31	26	
1.5	Rest		53	16	11.3	0.33	0.38	7.1	0.87			107			36			34	30	
2.0	Rest		58	15	17.0	0.50	0.56	9.6	0.90			107			37			34	31	
2.5	Rest		56	18	13.0	0.37	0.33	5.9	1.13			117			33			35	39	
3.0	Rest		55	16	11.4	0.31	0.28	5.1	1.13			117			33			36	41	
3.5	Unloaded	139/82	62	14	11.3	0.40	0.52	8.3	0.78			98			41			28	22	
4.0	Unloaded		59	19	13.2	0.47	0.58	9.9	0.81			98			42			28	23	
4.5	Unloaded		60	22	14.0	0.53	0.72	12.1	0.74			90			45			26	19	
5.0	Unloaded	136/78	62	20	15.9	0.60	0.72	11.6	0.84			97			43			26	22	
5.5	Unloaded		58	20	14.6	0.56	0.66	11.4	0.84			97			45			26	22	
6.0	Unloaded		59	21	16.8	0.60	0.67	11.4	0.90			100			43			28	25	
6.5	25	139/84	63	24	17.1	0.64	0.75	11.9	0.85			98			44			27	23	
7.0	25		63	24	17.1	0.64	0.75	11.9	0.85			98			44			27	23	
7.5	40		69	23	19.1	0.73	0.87	12.6	0.84			97			44			26	22	
8.0	55		69	26	23.4	0.87	0.94	13.6	0.93			103			42			27	25	
8.5	69	148/74	75	24	22.9	0.91	1.05	14.0	0.86			98			45			25	22	
9.0	84		78	24	24.5	1.02	1.11	14.3	0.91			99			45			24	22	
9.5	100		87	27	32.8	1.28	1.36	15.6	0.95			101			44			26	24	
10.0	114		107	28	40.0	1.59	1.66	15.5	0.96			102			44			25	24	
10.5	129	168/78	96	33	38.3	1.64	1.66	17.3	0.98			102			46			23	23	
11.0	144		111	26	43.3	1.83	1.76	15.8	1.04			103			46			24	25	
11.5	159	166/83	115	34	54.4	2.12	2.02	17.6	1.05			106			43			26	27	
12.0	173		113	31	50.8	2.16	2.06	18.2	1.05			104			46			24	25	
12.5	189		126	25	52.2	2.29	2.17	17.2	1.05			101			48			23	24	
13.0	203		136	23	64.3	2.73	2.41	17.7	1.13			105			46			24	27	
13.5	218	199/124	144	25	69.5	2.89	2.55	17.7	1.14			106			45			24	27	
14.0	233		150	29	80.3	3.19	2.71	18.1	1.18			109			44			25	30	
14.5	248		166	29	97.3	3.61	2.92	17.6	1.24			113			41			27	33	
15.0	Recovery	199/124	157	31	82.4	3.08	2.54	16.2	1.21			112			42			27	32	
15.5	Recovery		131	26	65.5	2.60	1.88	14.3	1.39			115			43			25	35	
16.0	Recovery		86	27	58.1	2.00	1.09	12.7	1.83			124			37			29	53	
16.5	Recovery		49	24	50.0	1.44	0.74	15.1	1.95			129			32			35	68	
17.0	Recovery		45	22	41.9	1.13	0.63	13.9	1.80			129			30			37	67	
17.5	Recovery		45	22	41.9	1.13	0.63	13.9	1.80			129			30			37	67	

Heart rate increased appropriately during exercise, as did the systemic blood pressure (Fig. 10.26.1 and Table 10.26.3). Abnormal findings were limited to postexercise bradycardia and asystole with loss of consciousness, consistent with the effects of a cardioinhibitory vasodepressive (vasovagal) reflex. Though vasovagal events are not unique to HCM, this is one of several mechanisms, along with tachyarrhythmias and abnormal baroreceptor reflexes, linked to syncope and/or sudden death in this condition.

Conclusion

Exercise capacity was normal, but the test elicited postexercise syncope due to asystolic pauses, likely reflecting abnormal ventricular mechanics and secondary reflex responses related to underlying HCM. Extensive data demonstrate that exercise testing is a relatively safe procedure.[1] This case is presented in part to illustrate that, although rare, serious complications can occur, and laboratories need to have plans for emergency medical response procedures.

REFERENCE

1. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010;122(2):191–225.

Case 27 Mitral Insufficiency

CLINICAL FINDINGS

This 43-year-old female electronics assembler had rheumatic fever at age 10. Over the 6 months prior to testing, she had developed increasing dyspnea and orthopnea, with intermittent atrial fibrillation and pleural effusion, requiring repeated hospitalizations. There was no evidence of mitral stenosis or coronary artery disease on catheterization, angiography, or echocardiography. At the time of exercise study, she had a sinus rhythm and findings of mitral regurgitation with left atrial and left ventricular enlargement but no pleural effusion or dependent edema. Her medications were digoxin, furosemide, and potassium chloride.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. She pedaled at 60 rpm without added load for 3 minutes, after which the work rate was increased 5 W per minute to her symptom-limited maximum. She stopped cycling because of general fatigue. There were no ST-segment changes or arrhythmia on ECG.

INTERPRETATION

Comments

Respiratory function at rest was compatible with a mild restrictive defect, but the diffusing capacity (DLCO) was normal (Table 10.27.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and anaerobic threshold were low (Table 10.27.2). See Flowchart 4 (Fig. 8.4). The breathing reserve was high (branch point 4.1). The ventilatory equivalent for CO_2 was close to the upper limit of normal or perhaps slightly elevated at the anaerobic threshold. If interpreted as elevated (at branch point 4.3), the flowchart leads to consideration of an abnormal pulmonary circulation, either due to primary pulmonary vascular disease or left heart failure. The striking findings are the low and flat O_2 pulse throughout exercise (Fig. 10.27.1, panel 2) and steep heart rate–$\dot{V}O_2$ relationship (Fig. 10.27.1, panel 3). These findings, along with low heart rate reserve, and low $\Delta\dot{V}O_2/\Delta WR$, are all indicative of heart disease. The low and unchanging O_2 pulse suggests that the patient's effective stroke volume was very low and the $C(a-\bar{v})O_2$ was maximized at a low work rate (Table 10.27.3). Note that if the $\dot{V}E/\dot{V}CO_2$ at the *AT* were instead interpreted as normal (branch point 4.3), the flowchart would also have led to heart disease through branch point 4.6. The difference reflects the extent to which the pulmonary circulation has been affected by the left-sided cardiac process.

Conclusion

This patient has marked exercise intolerance due to valvular heart disease associated with an inadequate forward cardiac output response to exercise (heart failure).

Table 10.27.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		43
Sex		Female
Height (cm)		160
Weight (kg)	61	56
VC (L)	2.88	2.03
IC (L)	1.92	1.49
TLC (L)	4.33	3.32
FEV_1 (L)	2.36	1.81
FEV_1/VC (%)	82	89
MVV (L/min)	90	90
DLCO (mL/mm Hg/min)	21.7	23.5

Table 10.27.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.57	0.79
Maximum heart rate (beats/min)	177	186
Maximum O_2 pulse (mL/beat)	8.9	4.2
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	5.6
AT (L/min)	>0.74	0.65
Maximum $\dot{V}E$ (L/min)		31
Exercise breathing reserve (L/min)	>15	59
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.8	31.6

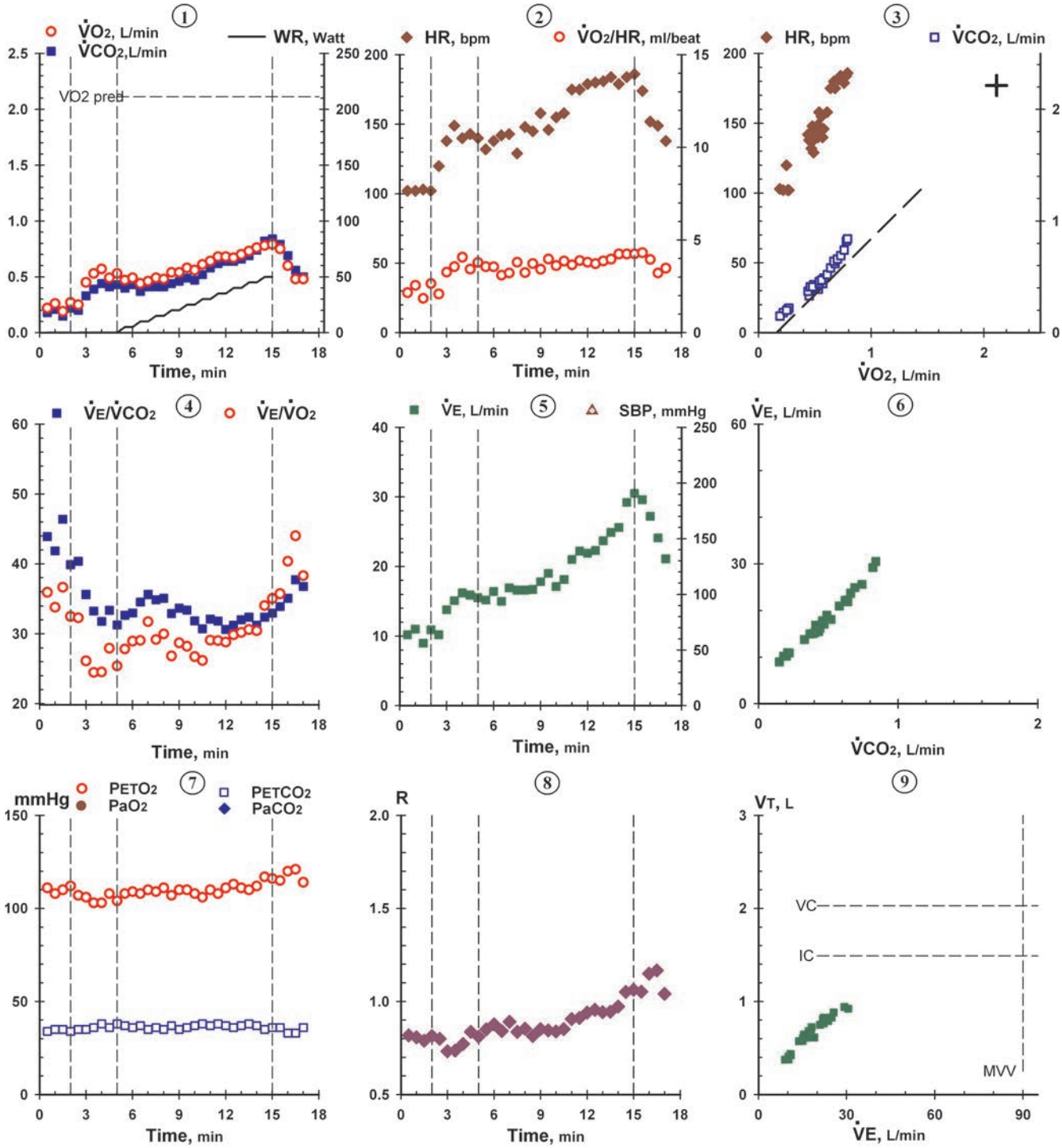

FIGURE 10.27.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 5 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.27.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest		102	27	10.2	0.18	0.22	2.2	0.82			111			34			44	36	
0.5	Rest		102	26	11.0	0.21	0.26	2.5	0.81			108			35			42	34	
1.0	Rest		103	24	9.0	0.15	0.19	1.8	0.79			110			35			46	37	
1.5	Rest		102	25	10.9	0.22	0.27	2.6	0.81			112			34			40	33	
2.0	Unloaded		120	25	10.2	0.20	0.25	2.1	0.80			107			35			40	32	
2.5	Unloaded		138	24	13.8	0.33	0.45	3.3	0.73			106			35			36	26	
3.0	Unloaded		149	25	15.1	0.39	0.53	3.6	0.74			103			36			33	24	
3.5	Unloaded		140	26	16.2	0.44	0.57	4.1	0.77			103			38			32	25	
4.0	Unloaded		143	26	15.9	0.41	0.49	3.4	0.84			108			36			33	28	
4.5	Unloaded		140	24	15.5	0.43	0.53	3.8	0.81			104			38			31	25	
5.0	5		132	25	15.2	0.40	0.47	3.6	0.85			108			37			33	28	
5.5	5		138	26	16.4	0.43	0.49	3.6	0.88			109			36			33	29	
6.0	10		142	26	15.0	0.37	0.44	3.1	0.84			108			37			35	29	
6.5	10		143	27	16.9	0.41	0.46	3.2	0.89			110			35			36	32	
7.0	15		129	27	16.6	0.41	0.49	3.8	0.84			109			36			35	29	
7.5	15		148	26	16.6	0.41	0.48	3.2	0.85			111			35			35	30	
8.0	20		145	26	16.7	0.44	0.54	3.7	0.81			107			37			33	27	
8.5	20		158	27	17.8	0.46	0.54	3.4	0.85			110			35			34	29	
9.0	25		146	31	19.0	0.49	0.58	4.0	0.84			110			36			33	28	
9.5	25		155	25	17.1	0.47	0.56	3.6	0.84			108			37			32	27	
10.0	30		158	25	18.1	0.52	0.61	3.9	0.85			106			38			31	26	
10.5	30		175	28	21.0	0.58	0.64	3.7	0.91			110			37			32	29	
11.0	35		175	29	22.2	0.62	0.68	3.9	0.91			108			38			32	29	
11.5	35		179	27	21.9	0.64	0.68	3.8	0.94			111			37			31	29	
12.0	40		180	28	22.3	0.64	0.67	3.7	0.96			113			36			31	30	
12.5	40		181	30	23.7	0.66	0.70	3.9	0.94			111			37			32	30	
13.0	45		184	30	24.9	0.69	0.73	4.0	0.95			110			38			32	31	
13.5	45		179	29	25.6	0.74	0.76	4.2	0.97			112			37			31	30	
14.0	50		184	31	29.2	0.82	0.78	4.2	1.05			117			35			32	34	
14.5	50		186	33	30.5	0.84	0.79	4.2	1.06			116			36			33	35	
15.0	Recovery		174	33	29.6	0.79	0.75	4.3	1.05			115			36			34	36	
15.5	Recovery		152	35	27.2	0.69	0.60	3.9	1.15			120			33			35	40	
16.0	Recovery		149	35	24.1	0.56	0.48	3.2	1.17			121			33			38	44	
16.5	Recovery		138	32	21.1	0.50	0.48	3.5	1.04			114			36			37	38	

Case 28 Congenital Heart Disease Surgically Corrected in Infancy

CLINICAL FINDINGS

This 21-year-old man had coarctation of the aorta and ventricular septal defect (VSD) identified at birth. In infancy, he underwent surgical repair of the coarctation and protective banding of the pulmonary artery, followed by a second procedure at 2 years of age to close the VSD and to release the pulmonary artery band. This procedure was complicated by complete heart block for which he received a permanent pacemaker. He had no specific restrictions as a child but was not athletic and was short of breath when running. He had minimal medical follow-up during his late teens. He was referred for exercise testing at the time of establishing care with an adult cardiologist who wished to quantify his functional capacity and evaluate him for possible biventricular pacing. He was working as a butcher and reported no difficulty in his daily activities, but he did not climb stairs or engage in sports. His only medication was carvedilol. He had a dual-chamber pacemaker operating in a VAT (ventricular paced, atrial sensed) mode. An echocardiogram performed just prior to referral had revealed the unexpected finding of global hypokinesis of the left ventricle with an ejection fraction of 35%. The right ventricle was enlarged with severe pulmonic valve regurgitation but normal estimated RV pressures. On physical examination, the cardiac impulse was displaced laterally and there were murmurs in both midsystole and mid-diastole; breath sounds were clear. There was no peripheral edema or clubbing. The ECG showed P waves preceding each paced QRS with a PR interval of 260 ms and a QRS of 140 ms consistent with right ventricular pacing.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer beginning with 3 minutes of pedaling at 60 rpm without resistance, followed by continuous increase in work rate at a rate of 15 W per minute. He ended the test at a work rate of 162 W with symptoms of leg fatigue. Heart rate increased progressively during exercise, without change in rhythm, and pulse oximetry remained normal.

Table 10.28.1

Selected Demographic Data

Measurement	Predicted	Measured
Age (years)		21
Sex		Male
Height (cm)		183
Weight (kg)		84

Comments

Demographic data are shown in Table 10.28.1. Pulmonary function tests were not available.

Analysis

The exercise data show significant exercise impairment for a man of this age, with a peak $\dot{V}O_2$ that was only around 60% of the reference value and a reduced anaerobic threshold (Table 10.28.2). Although peak heart rate was also lower than predicted, it is apparent that he exercised well beyond his *AT*, which was abnormally low, and attained an end-exercise R of 1.1 (Table 10.28.3 and Fig. 10.28.1, panel 8), so effort appears to have been good. The low peak heart rate was probably due to his β-blocker therapy, as there was no plateau to suggest attainment of the maximal rate allowed by the pacemaker programming. The slope of heart rate relative to $\dot{V}O_2$ (Fig. 10.28.1, panel 3) was normal up to the level of exercise performed reflecting intact sinus node function.

Table 10.28.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	3.59	2.18
Maximum heart rate (beats/min)	199	148
Maximum O_2 pulse (mL/beat)	18.1	16.0
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	9.7
AT (L/min)	>1.51	1.39
Blood pressure (mm Hg [rest, max ex])		120/-, 170/-
Maximum $\dot{V}E$ (L/min)		69
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	23.6	29.4

Table 10.28.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0.5	Rest	120/-	83	21	12.8	0.38	0.44	5.3	0.86			104			38			34	29	
1.0	Rest		85	22	16.0	0.46	0.52	6.1	0.89			108			36			35	31	
1.5	Rest		89	17	14.2	0.40	0.44	5.0	0.90			105			38			35	32	
2.0	Rest		84	21	13.8	0.39	0.46	5.4	0.87			107			37			35	30	
2.5	Rest		83	18	12.8	0.37	0.42	5.1	0.88			105			38			34	30	
3.0	Rest		86	18	14.3	0.41	0.45	5.2	0.91			108			36			35	32	
3.5	Unloaded		86	19	11.5	0.33	0.39	4.5	0.84			104			38			35	29	
4.0	Unloaded		93	29	15.4	0.42	0.48	5.1	0.88			107			37			37	32	
4.5	Unloaded		98	30	20.2	0.58	0.65	5.7	0.89			108			36			35	31	
5.0	Unloaded		100	32	20.7	0.61	0.73	7.3	0.84			105			37			34	29	
5.5	Unloaded		95	29	24.2	0.70	0.76	8.0	0.93			109			36			34	32	
6.0	Unloaded		93	29	21.8	0.67	0.80	8.6	0.84			104			37			32	27	
6.5	5		92	29	20.2	0.61	0.69	7.5	0.89			106			38			33	29	
7.0	13		92	29	22.2	0.69	0.79	8.5	0.88			106			37			32	28	
7.5	20		96	30	21.2	0.65	0.76	7.9	0.86			105			38			33	28	
8.0	27		96	31	22.6	0.97	0.76	7.9	0.89			107			37			34	30	
8.5	35		101	32	24.1	0.73	0.85	8.5	0.86			105			37			33	28	
9.0	43		100	28	23.4	0.75	0.89	8.9	0.84			103			39			31	26	
9.5	50		100	30	26.5	0.82	0.93	9.3	0.89			104			38			32	29	
10.0	57		106	34	29.7	0.94	1.06	10.0	0.89			106			37			32	28	
10.5	56		111	32	29.1	0.95	1.08	9.7	0.88			105			38			31	27	
11.0	72		108	32	34.5	1.10	1.17	10.8	0.95			109			37			31	30	
11.5	80		114	38	31.0	1.05	1.20	10.5	0.88			103			39			29	26	
12.0	87		120	35	36.8	1.22	1.29	10.8	0.94			108			38			30	28	
12.5	95		117	33	37.3	1.28	1.39	11.9	0.92			105			39			29	27	
13.0	103		122	37	44.9	1.49	1.51	12.4	0.99			110			37			30	30	
13.5	110		123	35	43.6	1.49	1.53	12.5	0.97			107			39			29	28	
14.0	118		131	38	46.2	1.57	1.58	12.0	1.00			109			38			29	29	
14.5	125		132	37	49.8	1.72	1.71	12.9	1.01			109			39			29	29	
15.0	132		136	36	51.0	1.79	1.74	12.8	1.02			109			39			29	29	
15.5	140		140	42	60.8	2.01	1.90	13.6	1.06			113			37			30	32	
16.0	148	170/-	142	40	61.9	2.06	1.92	13.5	1.07			113			37			30	32	
16.5	155		145	43	69.0	2.21	2.01	13.9	1.10			115			36			31	34	
17.0	162		148	45	68.8	2.19	1.98	13.4	1.11			115			35			31	35	
17.5	165		136	40	67.5	2.35	2.18	16.0	1.08			111			38			29	31	
18.0	Recovery		125	38	60.6	2.07	1.71	13.7	1.21			115			38			29	35	
18.5	Recovery		114	32	49.9	1.64	1.28	11.2	1.28			117			37			30	39	
19.0	Recovery		105	34	41.1	1.31	1.10	10.5	1.19			116			36			31	37	
19.5	Recovery		102	36	46.1	1.45	1.29	12.6	1.13			115			36			32	36	

With β-blockade in a healthy subject, this slope is usually shallow and the peak O_2 pulse is above predicted, reflecting a partially compensatory increase in stroke volume. In this case, peak O_2 pulse was low, implying that while the offsetting effects of systolic dysfunction and β-blockade preserved stroke volume early in exercise, peak stroke volume was less than normal. The ventilatory response to exercise was also mildly abnormal with $\dot{V}E/\dot{V}CO_2$ values slightly higher than the upper limit of normal (Table 10.28.2). The low peak $\dot{V}O_2$, peak O_2 pulse, and *AT* are consistent with cardiac dysfunction limiting maximal cardiac output, and the modestly elevated ventilatory equivalents suggest early impairment in pulmonary V:Q matching, even in the absence of overt findings of clinical heart failure.

Conclusion

Despite having early surgical therapy of congenital heart disease, this patient has significantly impaired exercise capacity, resulting from a number of residual or secondary processes. These include the development of left ventricular systolic dysfunction, pulmonic valve dysfunction, and conduction abnormalities. Typical of patients with congenital disorders, the extent of impairment was not evident from history alone.

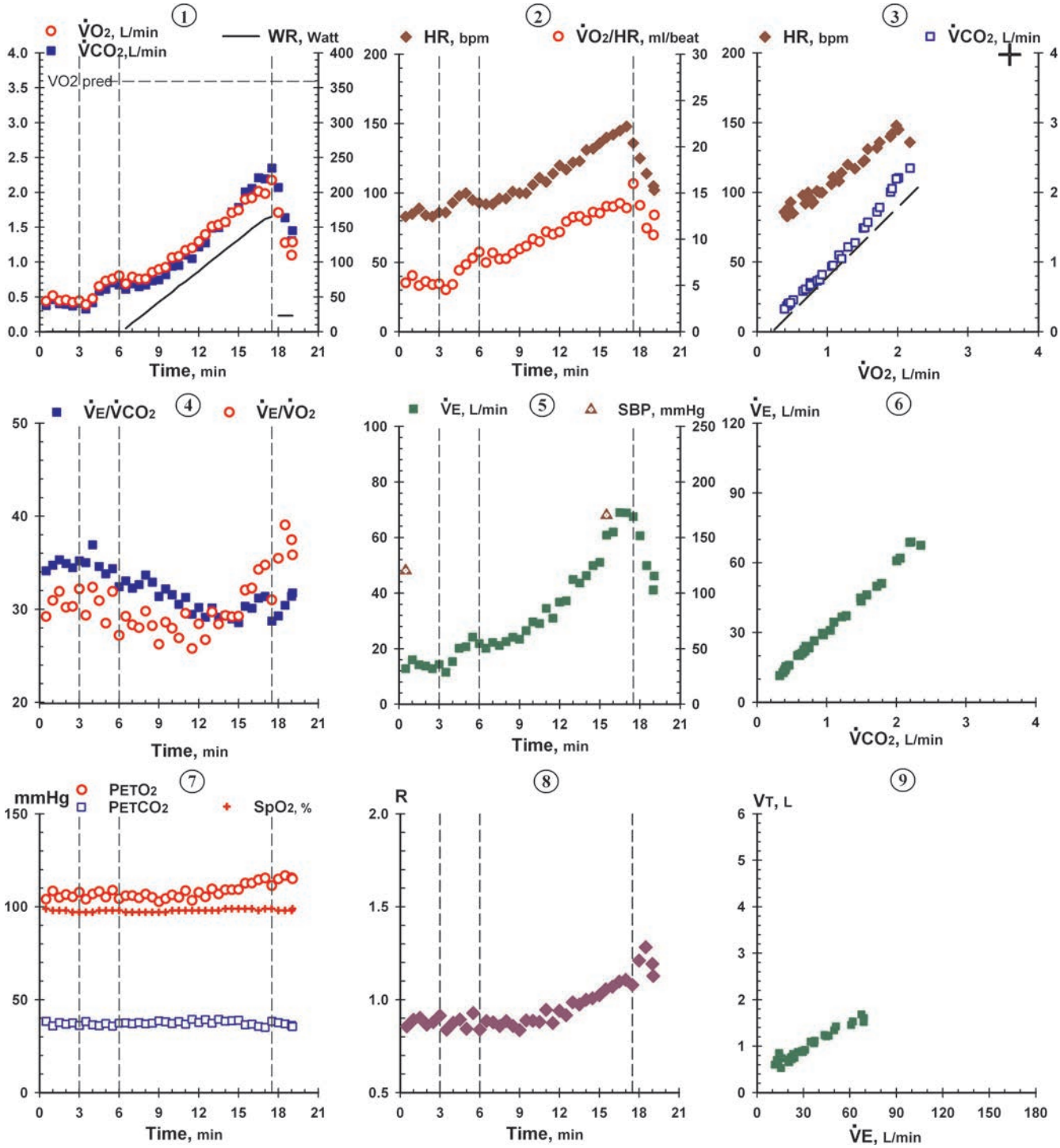

FIGURE 10.28.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 29 Congenital Heart Disease: Surgically Corrected Transposition of the Great Arteries

CLINICAL FINDINGS

This 22-year-old woman was referred for exercise testing as part of an evaluation for pulmonary hypertension identified on echocardiogram. She was born with transposition of the great vessels and was treated with a palliative atrial septostomy shortly after birth, followed by an arterial switch procedure at 2 years of age. She was not restricted in her activities as a child and took part in gym classes along with her peers. She did not participate in sports, however, and maintained a sedentary lifestyle. Evidence of pulmonary hypertension was first noted 3 years prior to this referral on a routine echocardiogram performed during pregnancy. The findings were more pronounced on a follow-up echocardiogram, with a dilated right ventricle and an estimated pulmonary artery systolic pressure of 60 mm Hg. She was therefore referred to a pulmonary hypertension specialist who requested exercise testing. She admitted to shortness of breath when ascending stairs, but did not think this was excessive. She denied syncope or chest pain. She was taking no medications. Examination was notable for a healed sternotomy scar, normal heart tones, and clear lung fields. There was no cyanosis, clubbing, or edema of the extremities. An ECG showed a sinus rhythm with right ventricular hypertrophy and diffuse ST-T wave changes.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer beginning with 3 minutes of pedaling at 60 rpm without resistance, followed by a continuous increase in work rate by 10 W per minute. She ended the test with the limiting symptom of leg fatigue. She also had shortness of breath, but denied chest pain or lightheadedness.

Comments

Resting pulmonary function, including lung mechanics and diffusing capacity were essentially normal (Table 10.29.1).

Analysis

Exercise capacity was low with the peak $\dot{V}O_2$ just over half of the predicted value and a similarly reduced *AT* (Table 10.29.2). Peak heart rate was less than the predicted maximum, but heart rate accelerated steeply during the last minute of exercise, associated with flat or declining O_2 pulse (Fig. 10.29.1, panels 2 and 3). Because hemoglobin concentration and oxygen saturation were normal, the flat O_2 pulse pattern implies that maximal stroke volume and $C(a-\bar{v})O_2$ were attained early in exercise and thereaf-

Table 10.29.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		22
Sex		Female
Height (cm)		150
Weight (kg)		55
Hemoglobin (mg/dL)		14.3
VC (L)	3.09	3.10
IC (L)	2.06	2.26
TLC (L)	4.17	4.29
FEV_1 (L)	2.74	2.46
FEV_1/VC (%)	89	79
MVV (L/min)	103	80
DLCO (mL/mm Hg/min)	23.8	21.5

Table 10.29.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.85	0.96
Maximum heart rate (beats/min)	198	141
Maximum O_2 pulse (mL/beat)	9.4	7.9
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	6.2
AT (L/min)	>0.77	0.57
Blood pressure (mm Hg [rest, max ex])		124/81, 195/151
Maximum $\dot{V}E$ (L/min)		31
Exercise breathing reserve (L/min)	>15	49
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.0	28.5

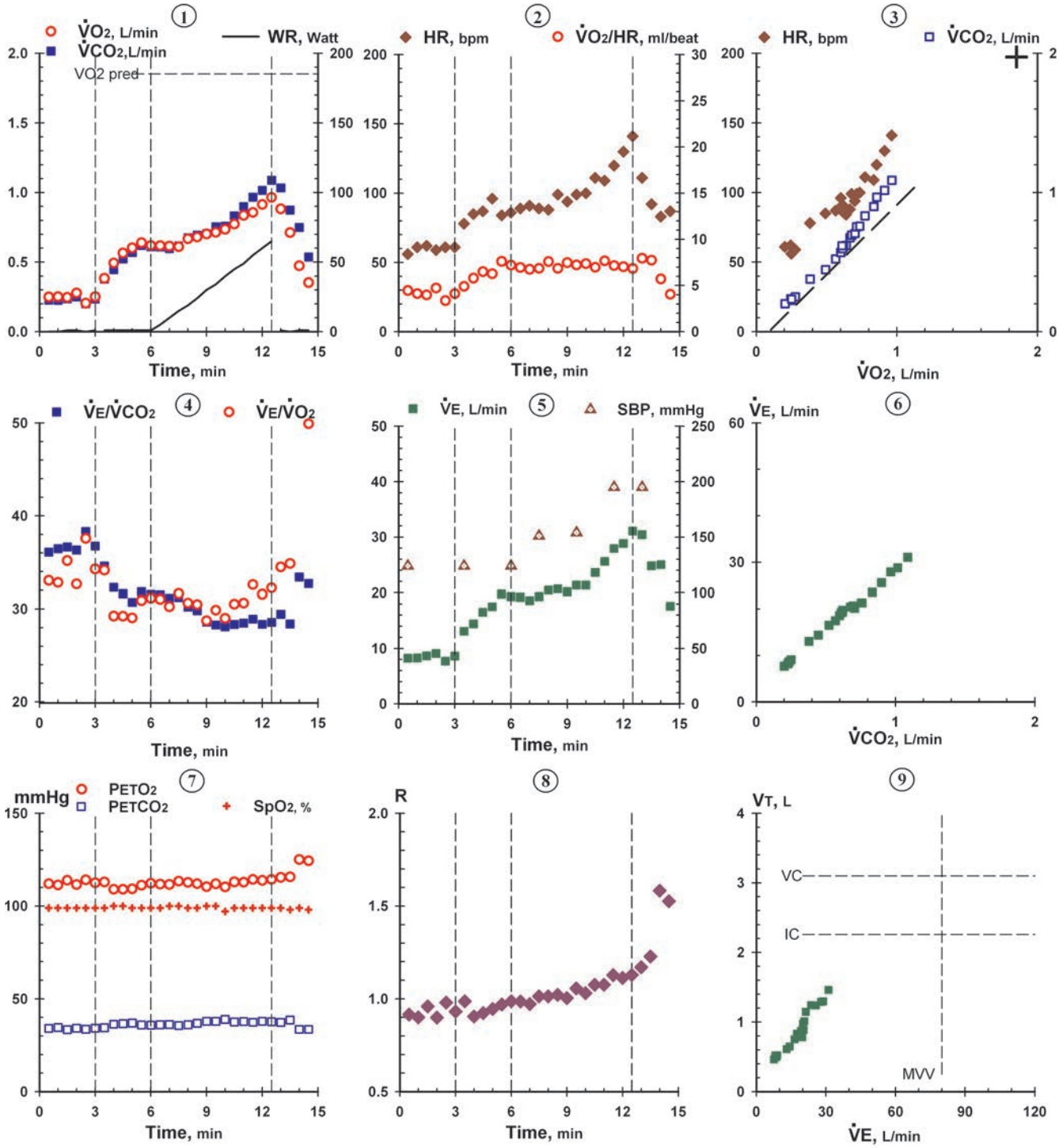

FIGURE 10.29.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.29.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0																				
0.5	Rest	124/81	56	16	8.2	0.23	0.25	4.4	0.92			112			34			36	33	
1.0	Rest		61	16	8.2	0.23	0.25	4.1	0.90			111			35			36	33	
1.5	Rest		62	17	8.7	0.24	0.25	4.0	0.96			114			33			37	35	
2.0	Rest		59	17	9.1	0.25	0.28	4.7	0.90			112			34			36	33	
2.5	Rest		61	17	7.7	0.20	0.21	3.4	0.98			114			34			38	38	
3.0	Rest		61	17	8.6	0.23	0.25	4.1	0.93			113			34			37	34	
3.5	Unloaded	124/81	78	21	13.1	0.38	0.38	4.9	0.99			113			34			35	34	
4.0	Unloaded		85	22	14.4	0.45	0.49	5.8	0.90			109			36			32	29	
4.5	Unloaded		87	22	16.5	0.52	0.57	6.5	0.92			109			37			32	29	
5.0	Unloaded		96	21	17.5	0.57	0.60	6.3	0.95			109			37			31	29	
5.5	Unloaded		84	25	19.7	0.62	0.64	7.6	0.97			111			36			32	31	
6.0	Unloaded		86	24	19.3	0.61	0.62	7.2	0.99			112			36			32	31	
6.5	5	124/81	89	24	19.2	0.61	0.62	6.9	0.99			112			36			31	31	
7.0	10		91	23	18.6	0.60	0.61	6.7	0.97			112			36			31	30	
7.5	15		89	22	19.3	0.62	0.61	6.9	1.01			113			36			31	32	
8.0	19	151/103	88	23	20.4	0.68	0.67	7.6	1.01			113			36			30	31	
8.5	24		99	21	20.7	0.69	0.68	6.9	1.02			112			37			30	30	
9.0	30		94	21	20.2	0.70	0.70	7.5	1.00			110			38			29	29	
9.5	34		99	19	21.3	0.71	0.71	7.2	1.06			112			38			28	30	
10.0	40	154/104	100	19	21.3	0.74	0.74	7.4	1.03			110			39			28	29	
10.5	45		111	19	23.6	0.83	0.77	7.0	1.08			113			38			28	31	
11.0	49		109	21	25.6	0.90	0.84	7.7	1.08			113			38			28	31	
11.5	55	195/151	120	22	27.9	0.97	0.86	7.1	1.13			114			37			29	33	
12.0	60		130	22	28.8	1.02	0.91	7.0	1.11			114			38			28	32	
12.5	65		141	21	31.1	1.09	0.96	6.8	1.13			114			38			29	32	
13.0	Recovery		111	24	30.4	1.03	0.88	7.9	1.17			115			37			29	34	
13.5	Recovery		92	20	24.8	0.87	0.71	7.7	1.23			116			39			28	35	
14.0	Recovery		83	22	25.0	0.75	0.47	5.7	1.58			125			35			33	53	
14.5	Recovery		87	15	17.6	0.54	0.35	4.0	1.53			124			34			33	50	

ter $\dot{V}O_2$ increased by heart rate alone. This is indicative of cardiovascular impairment. In contrast, variables related to ventilation and pulmonary gas exchange were normal. In particular, the $\dot{V}E/\dot{V}CO_2$ ratio decreased into the high 20s during exercise and oxygen saturation appeared normal (Table 10.29.3 and Fig. 10.29.1, panels 4 and 7), implying preserved V:Q matching. This is in contrast to the typical findings of patients with obliterative pulmonary vascular disease in whom $\dot{V}E/\dot{V}CO_2$ is usually elevated. Although pulmonary vascular disease does develop in a small percentage of patients after arterial switch procedures, the normal $\dot{V}E/\dot{V}CO_2$ ratios reflecting preserved pulmonary V:Q matching suggests that, in this case, the elevated pressures found on echocardiogram might actually reflect *right ventricular* hypertension without pulmonary vascular hypertension. The former can result from stenosis of the pulmonary outflow track at the site of the surgical anastomosis as a late complication of the procedure. The distinction could have important implications for treatment. The patient did not return for scheduled follow-up, so the nature of her central hemodynamic condition could not be confirmed.

Conclusions

Exercise tolerance was reduced by cardiovascular factors, but pulmonary gas exchange was well preserved in this patient with surgically treated congenital heart disease. The suspected cause of limitation and of her echocardiographic findings was pulmonary outflow track stenosis complicating the arterial switch procedure for transposition of the great arteries.

Case 30 Patent Ductus Arteriosus with Left-to-Right Shunt

CLINICAL FINDINGS

This 25-year-old man had recently developed exertional dyspnea and was found to have a patent ductus arteriosus (PDA). Cardiac catheterization demonstrated normal coronary arteries, a left ventricular ejection fraction of 56%, a large left-to-right shunt from the aorta through the patent ductus to the pulmonary artery, and normal pulmonary artery pressures at rest. The surgeon requested a preoperative cycle ergometer study with a pulmonary artery catheter in place to assess pulmonary artery pressures during exercise. The patient was sent to the exercise laboratory with a right radial artery and pulmonary artery catheters in place. Resting 12-lead ECGs showed left atrial enlargement and left ventricular hypertrophy.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 15 W per minute to tolerance. Intra-arterial pressures were recorded continuously, and blood was intermittently sampled from both the systemic arterial and pulmonary arterial catheters. The patient stopped exercise because of calf and thigh fatigue. He had no chest pain and no further ECG abnormalities.

Table 10.30.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		25
Sex		Male
Height (cm)		170
Weight (kg)	74	56
Hemoglobin (mg/dL)		14.6
VC (L)	4.39	4.27
IC (L)	2.93	2.42
TLC (L)	5.81	6.62
FEV_1 (L)	3.57	3.62
FEV_1/VC (%)	81	85
MVV (L/min)	156	158
DLCO (mL/mm Hg/min)	29.6	35.6

INTERPRETATION

Comments

Resting respiratory function studies were normal, with a high-normal DLCO suggestive of an increase in pulmonary capillary blood volume (Table 10.30.1). The systemic blood pressure was high during exercise, but the pulmonary artery pressure remained normal (Table 10.30.2). Of note, left ventricular output, calculated from the Fick equation using $C(a-\bar{v})O_2$ values derived from radial artery and right atrial blood samples, was considerably elevated relative to a given level of $\dot{V}O_2$ (data not shown).

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ and the anaerobic threshold were decreased (Table 10.30.2). Proceeding to Flowchart 4 (Fig. 8.4), the high breathing reserve (branch point 4.1), normal $\dot{V}E/\dot{V}CO_2$ (branch point 4.3), normal hematocrit (branch point 4.4), and low, unchanging O_2 pulse (branch point 4.6) lead to the category of heart disease. The ECG did not show evidence of myocardial ischemia, but the low $\Delta\dot{V}O_2/\Delta WR$ and steep heart rate (HR) versus $\dot{V}O_2$ indicate cardiovascular dysfunction. The pattern of the O_2 pulse throughout incremental exercise (Fig. 10.30.1, panel 2) indicates that the patient reached a maximum product of effective stroke volume and arterial–mixed venous O_2 difference $C(a-\bar{v})O_2$ early in the exercise study. This low O_2 pulse could be due to a low stroke volume or low $C(a-\bar{v})O_2$. Based on samples of central venous blood, $C(a-\bar{v})O_2$ values were high, reflecting a high total aortic blood flow, but this does not represent the $C(a-\bar{v})O_2$ across the lung, which would necessarily be lower due to the admixture of oxygenated shunt blood. Thus, the low O_2 pulse reflected a reduced effective $C(a-\bar{v})O_2$. The normal values for ventilatory equivalents, $P(A-a)O_2$ and VD/VT (Table 10.30.3) indicate that pulmonary V:Q matching was well maintained, arguing against significant pulmonary vascular disease.

Table 10.30.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.68	1.68
Maximum heart rate (beats/min)	195	166
Maximum O_2 pulse (mL/beat)	13.7	10.1
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.2
AT (L/min)	>1.09	1.00
Systematic blood pressure (mm Hg [rest, max])		154/70, 228/105
Pulmonary artery pressure (mm Hg [rest, max])		20/10, 30/15
Maximum $\dot{V}E$ (L/min)		54
Exercise breathing reserve (L/min)	>15	104
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	24.5	24.3
PaO_2 (mm Hg [rest, max ex])		103, 95
$P(A-a)O_2$ (mm Hg [rest, max ex])		6, 17
$PACO_2$ (mm Hg [rest, max ex])		39, 43
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		0, –3
VD/VT (rest, max ex)		0.39, 0.20
HCO_3^- (mEq/L [rest, 2-min recov])		25, 18

Conclusion

The large left-to-right shunt through the PDA obligates an increased left ventricular output to support the peripheral O_2 requirements at rest. With exercise, increased cardiac output is normally directed to the exercising muscle by restriction of blood flow to other vascular beds. In this case, however, blood flow to the exercising muscle was compromised by unregulated recirculation of part of the left ventricular output though the ductus left-to-right shunt. Thus, oxygen delivery to the peripheral tissues was inadequate for the demands of exercise. These abnormalities should be correctable by closing the ductus left-to-right shunt. Following surgical closure of the PDA, this patient's dyspnea and exercise tolerance improved considerably.

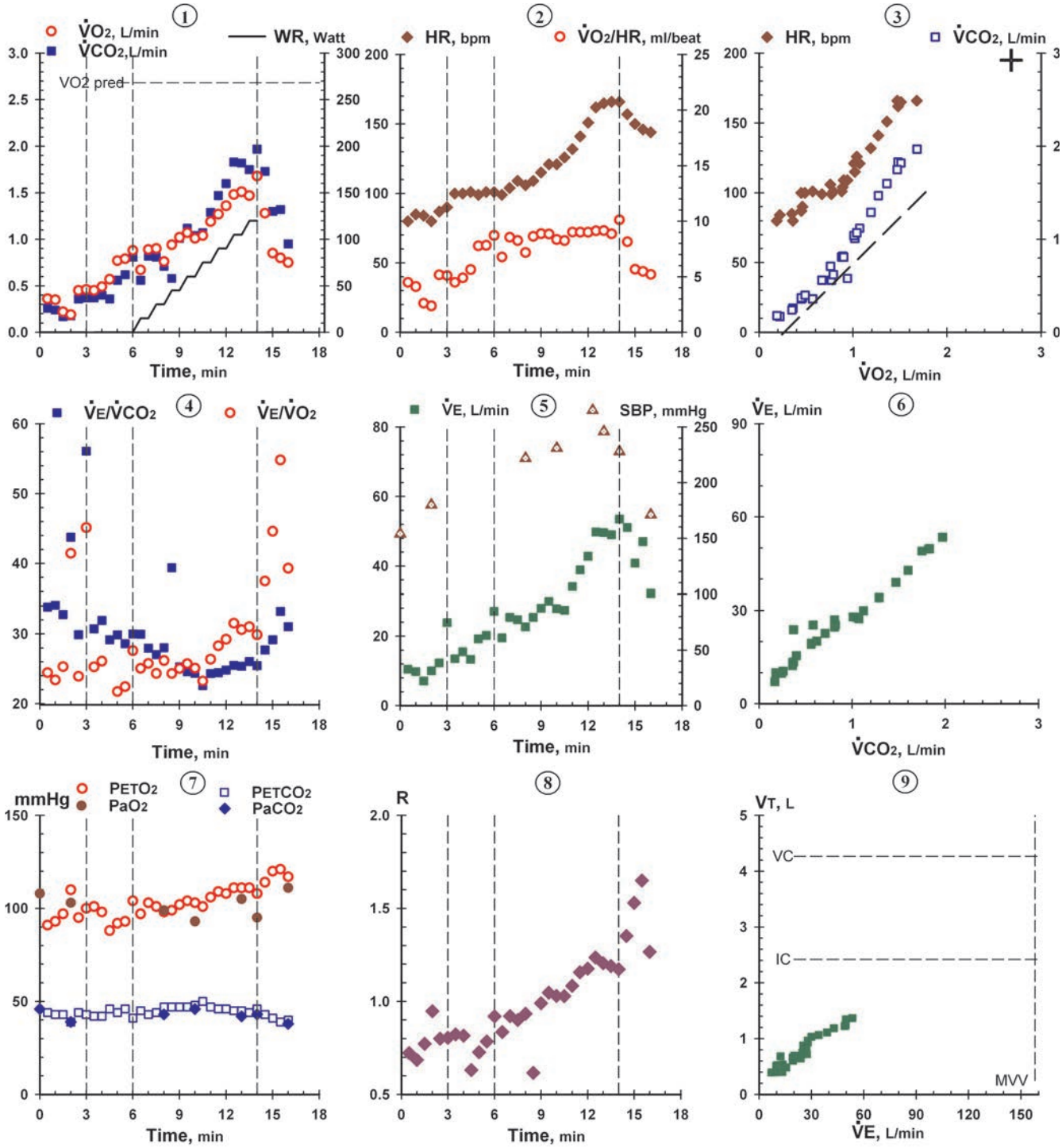

FIGURE 10.30.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.30.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	154/69								7.32	23		108			46				
0.5	Rest		80	20	10.5	0.26	0.36	4.5	0.72			91			44			34	24	
1.0	Rest		85	19	9.8	0.24	0.35	4.1	0.69			93			43			34	23	
1.5	Rest		84	18	7.1	0.17	0.22	2.6	0.77			97			43			33	25	
2.0	Rest	180/87	80	25	10.0	0.18	0.19	2.4	0.95	7.42	25	110	103	6	39	39	0	44	41	0.39
2.5	Rest		87	18	12.3	0.36	0.45	5.2	0.80			95			44			30	24	
3.0	Rest		90	37	23.9	0.37	0.46	5.1	0.80			100			43			56	45	
3.5	Unloaded		100	25	13.5	0.37	0.45	4.5	0.82			101			42			31	25	
4.0	Unloaded		100	32	15.5	0.40	0.49	4.9	0.82			98			42			32	26	
4.5	Unloaded		101	33	13.5	0.36	0.57	5.6	0.63			88			46			29	18	
5.0	Unloaded		99	29	19.2	0.56	0.77	7.8	0.73			92			44			30	22	
5.5	Unloaded		101	29	20.2	0.62	0.79	7.8	0.78			93			46			29	22	
6.0	Unloaded		101	33	27.1	0.81	0.88	8.7	0.92			104			41			30	28	
6.5	15		99	32	19.5	0.56	0.67	6.8	0.84			97			45			30	25	
7.0	15		104	29	25.4	0.82	0.89	8.6	0.92			103			43			28	26	
7.5	30		109	33	24.7	0.81	0.90	8.3	0.90			101			44			27	24	
8.0	30	222/102	106	33	22.7	0.71	0.76	7.2	0.93	7.39	26	98	99	6	47	43	–4	28	26	
8.5	45		109	30	25.4	0.58	0.94	8.6	0.62			99			47			39	24	
9.0	45		115	29	28.0	1.01	1.02	8.9	0.99			102			47			25	25	
9.5	60		121	29	30.0	1.12	1.07	8.8	1.05			104			47			25	26	
10.0	60	231/96	121	30	27.9	1.04	1.01	8.3	1.03	7.35	25	103	93	12	48	46	–2	24	25	
10.5	75		126	38	27.4	1.07	1.04	8.3	1.03			101			50			23	23	
11.0	75		132	32	34.1	1.29	1.19	9.0	1.08			106			47			24	26	
11.5	90		141	35	38.9	1.47	1.27	9.0	1.16			109			46			24	28	
12.0	90		151	36	42.8	1.69	1.36	9.0	1.18			108			46			25	29	
12.5	105		162	37	49.8	1.83	1.48	9.1	1.24			111			45			25	32	
13.0	105	246/108	165	40	49.6	1.82	1.51	9.2	1.21	7.34	22	111	105	9	45	42	–3	25	31	
13.5	120		166	40	49.0	1.75	1.47	8.9	1.19			111			44			26	31	
14.0	120	228/105	166	39	53.5	1.97	1.68	10.1	1.17	7.30	21	108	95	17	46	43	–3	25	30	
14.5	Recovery		157	37	51.1	1.73	1.28	8.2	1.35			114			43			28	37	
15.0	Recovery		150	34	40.8	1.30	0.85	5.7	1.53			120			41			29	45	
15.5	Recovery		146	37	47.0	1.32	0.80	5.5	1.65			121			39			33	55	
16.0	Recovery	171/90	144	32	32.2	0.95	0.75	5.2	1.27	7.29	18	117	111	7	40	38	–2	31	39	

Case 31 Patent Ductus Arteriosus with Right-to-Left Shunt (Eisenmenger Ductus)

CLINICAL FINDINGS

This 37-year-old woman was identified as having a patent ductus arterious (PDA) as a child but had not undergone surgical repair. In early adulthood, she was told she had pulmonary hypertension. She reports being normally active while growing up and being able to ride a bicycle. Her sister describes her as less active than her peers, however, and having been protected from vigorous activities by her parents. She had worked for several years as an accountant but quit work at her parents' urging, out of concern for her health. She stated that she could walk on level ground for extended periods at her own pace and ascend the stairs to her third floor apartment. She identified fatigue as her primary limiting symptom in her daily activities. She denied cough, wheezing, or syncope, but sometimes noted cyanosis of her fingers. She was a nonsmoker but had exposure to secondhand smoke as a child. On exam, she was thin, with reduced muscle mass. Breath sounds were clear and cardiac examination was notable for a prominent S2 and a III/VI holosystolic murmur. There was cyanosis and clubbing of the toes but not of the fingers. While seated at rest, pulse oximeter readings from the fingers of either hand were 93% to 94% and the toes were 60% to 65% bilaterally.

EXERCISE FINDINGS

Exercise testing was performed on a cycle ergometer. After pedaling at 60 rpm for 3 minutes, the work rate was increased continuously by 10 W per minute until the patient stopped with symptoms of leg fatigue. Pulse oximetry was monitored on a right-hand finger and read 94% to 95% at rest and during the first several minutes of exercise. Thereafter, there was progressive decline in estimated saturation to 85% at end exercise with further decrease in the first 1 to 2 minutes of recovery.

Table 10.31.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		37
Sex		Female
Height (cm)		166
Weight (kg)		49
VC (L)	3.91	1.96
IC (L)	2.36	1.53
FEV_1 (L)	3.22	0.95
FEV_1/VC (%)	83	48
MVV (L/min)	108	39

INTERPRETATION

Comments

The differential cyanosis noted on physical examination is characteristic of PDA with a reversal of shunt due to pulmonary hypertension. A recent echocardiogram had demonstrated right ventricular hypertrophy, large PDA, and estimated pulmonary artery pressures at systemic levels. Spirometry showed a moderate ventilatory defect, which was partially due to airflow obstruction (Table 10.31.1).

Analysis

Peak $\dot{V}O_2$ and anaerobic threshold were both reduced (Table 10.31.2). The abnormalities in the $\dot{V}O_2$ response to exercise are strikingly evident in the graphical displays (Fig. 10.31.1), which demonstrate an abnormally slow increase in $\dot{V}O_2$ relative to work rate (panel 1) and subsequent delayed decrease in $\dot{V}O_2$ toward baseline in the recovery period. This indicates severely impaired oxygen delivery to the exercising muscle. The O_2 pulse (panel 2) increased only marginally with ex-

Table 10.31.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.48	0.60
Maximum heart rate (beats/min)	183	157
Maximum O_2 pulse (mL/beat)	8.1	4.4
$\Delta\dot{V}O_2/\Delta WR$, (mL/min/W)	10.3	3.5
AT (L/min)	>0.68	0.50
Blood pressure (mm Hg [rest, max])		104/77, 175/105
Maximum $\dot{V}E$, (L/min)		24
Exercise breathing reserve (L/min)	>15	15
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.9	38.6
O_2 saturation, finger pulse oximetry (% [rest, max])		95, 85

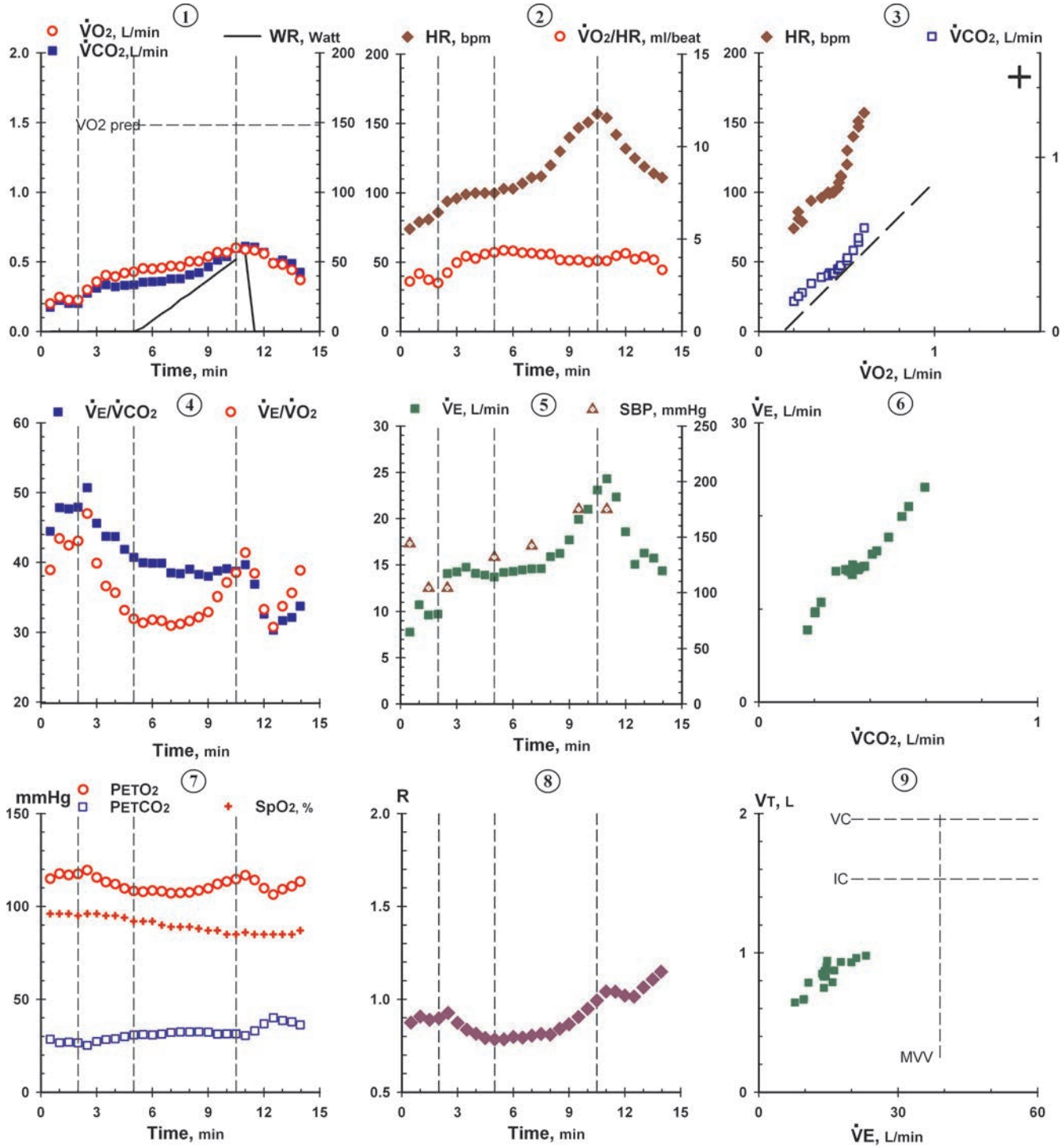

FIGURE 10.31.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $P_{ET}CO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

ercise and actually decreased during the latter half of incremental work. This corresponds to the very steep increase in heart rate relative to $\dot{V}O_2$ (panel 3). Ventilation in response to exercise was higher than normal, as reflected in high $\dot{V}E/\dot{V}CO_2$ at the *AT* (panel 4) and steep slope of $\dot{V}E$ relative to $\dot{V}CO_2$ (panel 6). This is consistent with high V:Q due to pulmonary vascular disease, which is intrinsic to Eisenmenger syndrome. The pattern of ventilation at the start of exercise differed from findings commonly observed with central circulatory right-to-left shunting, however, in that there was no acute increase in the ventilatory equivalents or decrease in end-tidal PCO_2. This is consistent with the ductus arteriosus being distal to the take off of the carotid arteries, so that desaturation associated with right-to-left shunting affected blood flowing to the lower extremities, but not blood flow to the carotid and central chemoreceptors. Nevertheless, this patient had gradual desaturation on finger pulse oximetry. Because the brachial artery blood flow should leave the aorta proximal to the ductus, the exercise desaturation likely resulted from nonshunt mechanisms related to pulmonary vascular disease and very low central venous oxygenation. The finger oximeter readings do not reflect the more severe desaturation of the lower extremity blood flow.

As with the patient presented as Case 30 in this chapter, $\dot{V}O_2$ abnormalities resulted from impaired oxygen delivery to the exercising muscle due to a PDA. In the present case, the impairment was attributable to both the low O_2 content of the blood and the effect of pulmonary vascular disease on cardiac output, whereas in Case 30, it resulted from inability to regulate distribution of blood with normal O_2 content to the legs. Despite the abnormal lung function and moderately increased ventilatory equivalents observed in the test performed by the present patient, she had a breathing reserve at end exercise, and ended the test with leg fatigue, so she did not appear to be ventilatory limited.

Conclusion

This patient has severe exercise impairment due to the effects of reduced cardiac output due to pulmonary vascular disease and reduced arterial oxygen content due to right-to-left shunt. The latter is underestimated by her upper extremity pulse oximetry, and does not result in the typical ventilatory responses of a central shunt (as illustrated in Case 36 of this chapter) due to the location of the PDA, which does not direct shunted blood to the ventilatory control centers.

Table 10.31.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{VD}{VT}$
												ET	*a*	(*A* − *a*)	*ET*	*a*	(*a* − *ET*)			
	Rest	144/105																		
0.5	Rest		74	12	7.8	0.18	0.20	2.7	0.88			115			29			44	39	
1.0	Rest		79	14	10.7	0.22	0.25	3.1	0.91			118			27			48	43	
1.5	Rest	104/77	81	15	9.6	0.20	0.23	2.8	0.89			117			27			48	42	
2.0	Rest		86	15	9.7	0.20	0.23	2.6	0.90			118			27			48	43	
2.5	Rest		94	19	14.1	0.28	0.30	3.2	0.93			120			25			51	47	
3.0	Unloaded		96	17	14.2	0.31	0.36	3.7	0.87			116			27			46	40	
3.5	Unloaded		99	16	14.7	0.34	0.40	4.1	0.84			113			28			44	37	
4.0	Unloaded		100	17	14.1	0.32	0.40	4.0	0.82			112			29			44	36	
4.5	Unloaded		100	17	13.9	0.33	0.42	4.2	0.79			110			30			42	33	
5.0	Unloaded		100	16	13.7	0.34	0.43	4.3	0.79			108			31			41	32	
5.0	Unloaded	132/87	100	16	13.7	0.34	0.43	4.3	0.79			108			31			41	32	
5.5	3		103	16	14.2	0.36	0.45	4.4	0.79			108			31			40	31	
6.0	8		103	17	14.3	0.36	0.45	4.4	0.80			109			31			40	32	
6.5	13		107	17	14.4	0.36	0.46	4.3	0.79			108			31			40	32	
7.0	17	142/88	111	16	14.6	0.38	0.47	4.2	0.80			107			32			38	31	
7.5	23		112	16	14.6	0.38	0.47	4.2	0.81			107			32			38	31	
8.0	27		120	20	15.9	0.41	0.50	4.2	0.81			108			32			39	32	
8.5	32		130	19	16.2	0.42	0.50	3.9	0.84			109			33			38	32	
9.0	37		140	19	17.7	0.47	0.54	3.8	0.87			110			32			38	33	
9.5	42	175/82	147	21	19.9	0.51	0.57	3.9	0.90			112			31			39	35	
10.0	47		151	22	21.0	0.54	0.57	3.8	0.95			113			31			39	37	
10.5	52		157	24	23.1	0.60	0.60	3.8	0.99			115			31			39	38	
11.0	56	175/82	154	25	24.3	0.61	0.59	3.8	1.04			117			31			40	41	
11.5	Recovery		142	20	22.3	0.61	0.58	4.1	1.04			114			33			37	38	
12.0	Recovery		132	16	18.6	0.57	0.56	4.2	1.02			110			37			33	33	
12.5	Recovery		125	15	15.0	0.50	0.49	3.9	1.01			106			40			30	31	
13.0	Recovery		119	15	16.3	0.51	0.48	4.1	1.06			109			39			32	34	
13.5	Recovery		114	15	15.7	0.49	0.44	3.9	1.11			111			38			32	36	
14.0	Recovery		111	16	14.4	0.43	0.37	3.3	1.15			113			36			34	39	

Case 32 Eisenmenger Complex (Ventricular Septal Defect with Pulmonary Hypertension)

CLINICAL HISTORY

This 42-year-old man was known to have a ventricular septal defect (VSD) from birth. Surgery was recommended at the age of 7 years, but his family declined. He had only intermittent medical follow-up until several months prior to this evaluation when he was hospitalized for lower extremity edema and shortness of breath. These improved with nocturnal supplemental oxygen, and he was referred for exercise testing as part of his evaluation for pharmacologic treatment of his pulmonary hypertension. He reported that he always needed to do activities more slowly than others his age. He never had syncope or lightheadedness and described his cardiac symptoms as "anxiousness" and shortness of breath. He worked as a cashier and became dyspneic with sustained walking on level ground. He did not know if he was able to climb stairs. At the time of this test, his only medications were warfarin and nighttime oxygen. Examination was notable for obesity and plethora with mild cyanosis of the lips and clubbing of the fingers. On cardiac auscultation, the S2 was loud and there was a holosystolic murmur. There was no peripheral edema. An ECG showed a sinus rhythm and right ventricular hypertrophy. Pulse oximetry while seated at rest ranged from 84% to 86%

EXERCISE FINDINGS

Exercise was performed on a cycle ergometer. After 3 minutes of unloaded cycling, the work rate was increased continuously by 10 W per minute until the patient stopped with symptoms of leg fatigue. Shortly after the start of exercise, pulse oximeter readings began to decrease gradually, reaching a nadir of 77% at the end of the test (Fig. 10.32.1, panel 7). There were no significant changes in the ECG.

Table 10.32.1

Selected Clinical Data

Measurement	Predicted	Measured
Age (years)		42
Sex		Male
Height (cm)		175
Weight (kg)		95

INTERPRETATION

Comment

Demographic characteristics are shown in Table 10.32.1. Pulmonary function tests were not available.

Analysis

The peak $\dot{V}O_2$ and the anaerobic threshold were severely reduced relative to what was predicted (Table 10.32.2). There was a large heart rate reserve and both $\dot{V}O_2$ and O_2 pulse continued to increase at the time the test was ended, raising the question of whether the test reflected maximal effort. Whether or not effort was absolutely maximal, the low anaerobic threshold and abnormal slope of $\Delta\dot{V}O_2/\Delta WR$ (Table 10.32.2 and Fig. 10.32.1, panel 1) indicate impaired oxygen delivery even in the submaximal range of effort. The ventilatory response to exercise was higher than normal, with little or no decrease in the value of the ventilatory equivalents as the patient progressed from rest to exercise, and an abnormally high value of around 37 at the *AT* (Table 10.32.3 and Fig. 10.32.1, panel 4). This indicates a failure to decrease V_D/V_T normally with exercise. Progressively, greater arterial desaturation appeared to begin about 30 seconds after starting exercise (Fig. 10.32.1, panel 7). These findings are consistent with abnormal pulmonary gas exchange due to V:Q mismatch and right-to-left shunt, which impair oxygenation and the clearance of metabolic CO_2. Interestingly,

Table 10.32.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.82	1.00
Maximum heart rate (beats/min)	178	100
Maximum O_2 pulse (mL/beat)	15.8	10.0
$\Delta\dot{V}O_2/\Delta WR$, (mL/min/W)	10.3	6.7
AT (L/min)	>1.25	0.63
Blood pressure (mm Hg [rest, max])		128/67, 158/87
Maximum $\dot{V}E$, (L/min)		39
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.1	37.0
O_2 saturation, finger pulse oximetry (% [rest, max])		86, 77

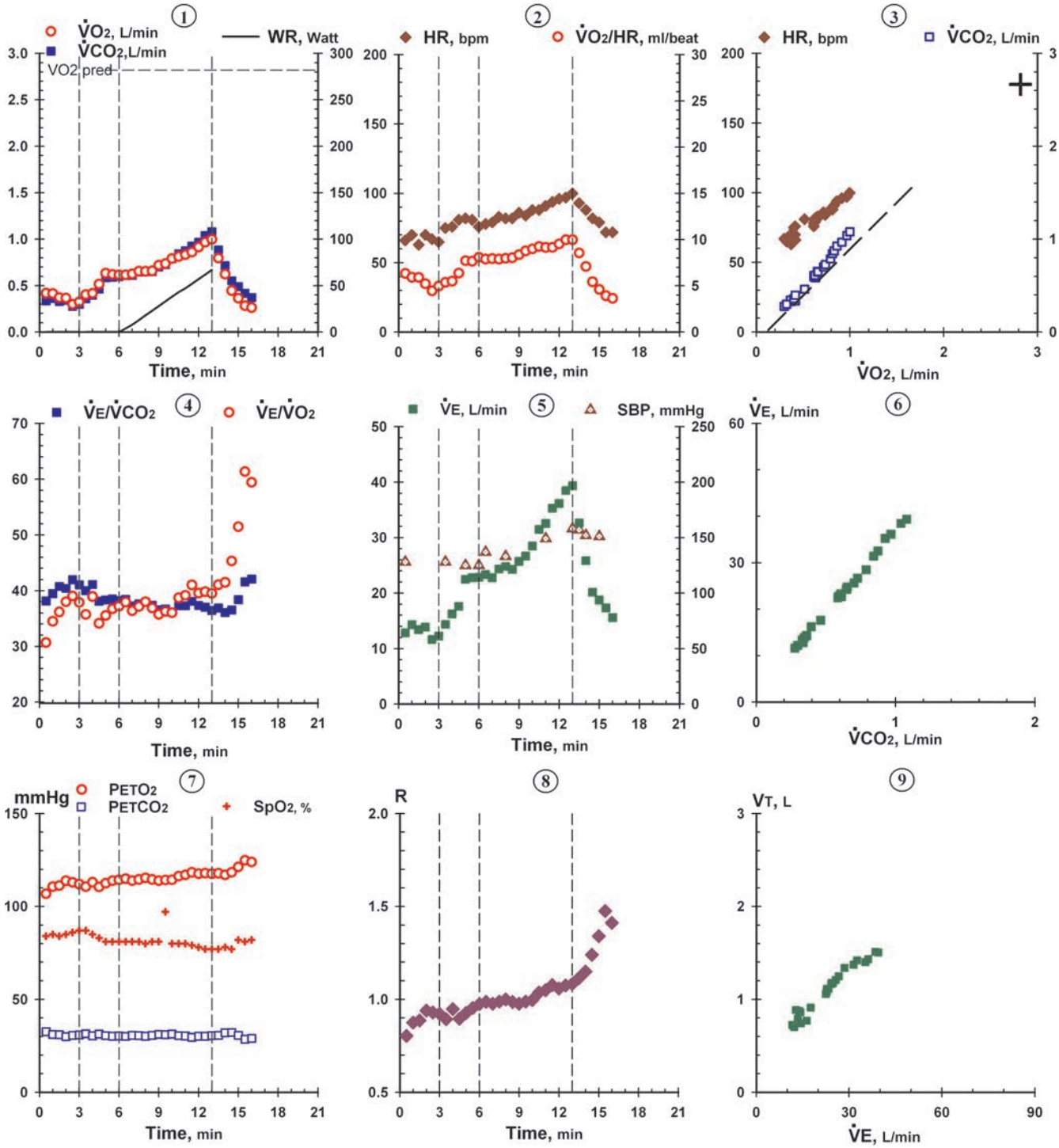

FIGURE 10.32.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

the acute ventilatory changes typically associated with an exercise-induced increase in right-to-left shunting were not clearly demonstrated on this test (an example of this is presented as Case 36 in this chapter), suggesting that there was little change in the intracardiac shunt at the start of exercise. Progressive arterial desaturation would be expected during exercise even with no change in the shunt fraction due to decreasing central venous oxygen saturation. However, shunt fraction often varies dynamically during exercise as well, dictated by the relative resistances to flow through pulmonary and systemic circulations.

Conclusion

This patient with Eisenmenger complex has severely reduced exercise capacity and gas exchange abnormalities consistent with pulmonary vascular disease and central right-to-left shunt.

Table 10.32.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	*a*	*(A − a)*	*ET*	*a*	*(a − ET)*			
0																				
0.5	Rest	128/67	66	15	12.8	0.34	0.42	6.3	0.80			107			33			38	31	
1.0	Rest		70	17	14.3	0.36	0.41	5.9	0.87			111			31			39	34	
1.5	Rest		63	17	13.4	0.33	0.37	5.9	0.89			111			31			41	36	
2.0	Rest		70	16	13.9	0.34	0.37	5.2	0.94			114			30			40	38	
2.5	Rest		67	16	11.6	0.28	0.30	4.4	0.93			113			31			42	39	
3.0	Rest		65	17	12.2	0.30	0.32	5.0	0.92			112			31			41	38	
3.5	Unloaded	128/67	75	19	14.4	0.36	0.40	5.4	0.89			111			31			40	36	
4.0	Unloaded		76	21	16.2	0.40	0.42	5.5	0.95			113			30			41	39	
4.5	Unloaded		81	19	17.6	0.46	0.52	6.4	0.90			111			31			38	34	
5.0	Unloaded	125/77	82	21	22.5	0.59	0.63	7.7	0.93			113			30			38	36	
5.5	Unloaded		81	21	22.8	0.59	0.62	7.7	0.95			114			30			39	37	
6.0	Unloaded		76	21	22.8	0.60	0.61	8.1	0.97			114			30			38	37	
6.5	4	137/73	78	21	23.3	0.61	0.62	7.9	0.99			115			30			38	38	
7.0	8		79	21	22.8	0.61	0.63	7.9	0.98			114			31			37	36	
7.5	13		83	21	24.3	0.65	0.66	7.9	0.99			115			31			38	37	
8.0	18	133/78	82	21	24.8	0.65	0.65	8.0	1.00			115			30			38	38	
8.5	23		82	21	24.3	0.65	0.66	8.0	0.99			115			31			37	37	
9.0	28		86	21	25.7	0.70	0.72	8.4	0.98			114			31			37	36	
9.5	33		84	21	26.7	0.73	0.74	8.8	0.99			114			31			37	36	
10.0	38		88	21	28.5	0.79	0.79	9.0	1.00			114			31			36	36	
10.5	43		88	23	31.5	0.84	0.81	9.2	1.04			116			30			37	39	
11.0	47	149/78	91	23	32.6	0.87	0.83	9.1	1.05			117			30			37	39	
11.5	52		94	25	35.3	0.93	0.86	9.1	1.08			118			30			38	41	
12.0	57		96	25	36.1	0.97	0.91	9.5	1.06			118			30			37	40	
12.5	62		97	26	38.5	1.04	0.97	10.0	1.07			118			30			37	40	
13.0	67	158/84	100	26	39.4	1.08	1.00	10.0	1.08			118			31			36	39	
13.5	Recovery	157/84	93	26	32.6	0.88	0.79	8.5	1.11			118			31			37	41	
14.0	Recovery		88	23	25.8	0.72	0.62	7.1	1.15			117			32			36	41	
14.5	Recovery		82	21	20.2	0.55	0.45	5.4	1.24			118			32			37	45	
15.0	Recovery	151/79	79	22	18.7	0.49	0.36	4.6	1.34			121			31			38	51	
15.5	Recovery		72	21	17.3	0.42	0.28	3.9	1.48			125			29			42	61	
16.0	Recovery		72	21	15.6	0.37	0.26	3.6	1.41			124			29			42	59	

Case 33 Early Onset of Exercise Lactic Acidosis: Differentiating Circulatory from Muscular Impairment

CLINICAL FINDINGS

This 29-year-old male executive presented with about a 1-year history of exercise intolerance due to fatigue, dyspnea, and lightheadedness associated with exertion. He had a history of incompletely reversible asthma, but evaluation by his pulmonologist, allergist, and cardiologist, including an unremarkable echocardiogram, failed to identify the cause of his symptoms. He was referred for cardiopulmonary exercise testing to better define the pathophysiology of his symptoms.

All together, three tests were performed by this patient. His initial exercise test was performed without blood sampling. This showed that peak $\dot{V}O_2$, anaerobic threshold, $\Delta\dot{V}O_2/\Delta WR$, and O_2 pulse were all reduced, but the basis for this was unclear. A second test was done with arterial blood gas sampling. This showed similar results to the noninvasive test and confirmed that the noninvasively determined anaerobic threshold represented early onset of lactic acidosis. Although this test also demonstrated abnormal V_D/V_T, consistent with his known airway disease, he did not appear clearly ventilatory limited, and this seemed unlikely to account for the degree of reduction in the peak $\dot{V}O_2$ and *AT*. Also, there were no ischemic ECG changes or arrhythmia to account for his impairment. He was thus suspected to have either a circulatory problem with a reduced stroke volume or, less likely, a skeletal muscle myopathy in which the muscles could not consume O_2 normally.

To distinguish between a cardiovascular disorder and a muscle bioenergetic problem, a third exercise test was performed. On this occasion, testing was conducted with brachial arterial, pulmonary arterial, and femoral venous catheters, the latter directed caudally, in place. Cardiac output and stroke volume were determined by the direct Fick method using arterial and central venous O_2 measurements to assess the adequacy of O_2 delivery, and critical capillary PO_2 was determined from the femoral venous O_2 saturation, content, and PO_2 to assess the ability of the muscles to extract and utilize O_2. In addition, direct arterial blood pressure was recorded. This test is presented in detail here.

EXERCISE FINDINGS

Two catheters were placed in the right femoral vein: one directed into the pulmonary artery and one directed caudally for sampling of muscle venous blood. A third catheter was placed in the brachial artery for the purpose of measuring blood gases, lactate, and arterial pressures and wave forms. The patient performed exercise on a cycle ergometer while breathing through a mouthpiece, with nose occluded, for breath-by-breath measurements of gas exchange. Heart rate and rhythm were continuously monitored. The protocol consisted of 3 minutes of rest and 3 minutes of unloaded pedaling at 60 rpm, followed by a progressive increase in work rate of 20 W per minute until the patient became too symptomatic to continue. Blood was sampled for blood gases, pH, and lactate at rest, at the end of 3 minutes of unloaded cycling, periodically during the incremental exercise period, and at 6 minutes of recovery, from the three sites. Twelve-lead ECG recordings were obtained during rest, exercise, and recovery. The patient performed the exercise test with good effort. His resting and exercise ECGs were normal, and there was no cardiac ectopy.

The patient had a near-syncopal event during preexercise spirometry and again in the immediate recovery period. During these events, he complained of dizziness and was diaphoretic. Similar symptoms had occurred previously after exercise, including the two prior exercise tests performed in the laboratory. On this occasion, his blood pressure was noted to drop to 82/64 soon after exercise ended, whereas his pulse remained around 90 bpm. Lying flat with his legs raised helped him recover from these episodes. The typical cardiac slowing of a vasovagal event was not observed.

INTERPRETATION

Comments

Respiratory function tests showed moderate airflow obstruction with a normal D_{LCO} (Table 10.33.1).

Analysis

Referring to Tables 10.33.2 and 10.33.3 and Flowchart 1 (Fig. 8.1), his peak $\dot{V}O_2$ and anaerobic threshold were both low, bringing us to Flowchart 4 (Fig. 8.4). The breathing reserve was relatively small but still normal (branch point 4.1), and the ventilatory equivalent for $\dot{V}CO_2$ at the anaerobic threshold (branch point 4.3), was borderline normal, leading to the category of O_2 flow problem of nonpulmonary origin. The hematocrit was normal (branch point 4.4), and he had a low O_2 pulse that remained nonchanging as peak $\dot{V}O_2$ was approached. This suggests heart disease. Although his ECG was normal, he had an abnormally steep heart rate increase relative to $\dot{V}O_2$ increase (Fig. 10.33.1, panel 3), and a reduced $\Delta\dot{V}O_2/\Delta WR$, supporting the diagnosis of heart disease.

Hemodynamic measurements are shown in Table 10.33.4. The cardiac output, calculated by the Fick method, increased at the expected rate relative to the increase in $\dot{V}O_2$ during exercise (normally 5 to 6 L per minute of cardiac output for each liter per minute increase in $\dot{V}O_2$), but the ab-

Table 10.33.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		29
Sex		Male
Height (cm)		180
Weight (kg)	81	86
Hematocrit (%)		47
VC (L)	4.95	4.29
IC (L)	3.30	2.94
FEV_1 (L)	4.13	2.74
FEV_1/VC (%)	83	64
MVV (L/min)	163	110
DLCO (mL/mm Hg/min)[a]	34.6	31.6

[a]Measured on a separate occasion.

solute value was lower than expected at rest and at all levels of $\dot{V}O_2$, with a peak cardiac output of only 10 L per minute. Accordingly, the calculated stroke volume was abnormally low, starting at 44 mL at rest and increasing to only about 65 mL per beat during exercise. These findings identified inadequate blood flow as the basis for the low peak $\dot{V}O_2$ and steep heart rate–$\dot{V}O_2$ relationship. O_2 extraction was normal both across the leg (normal critical capillary PO_2) and across the entire systemic circulation. The maximum O_2 extraction (75% to 80%) was reached at a lower $\dot{V}O_2$ than expected due to the reduced cardiac output. Normal extraction of O_2 across the leg excluded a skeletal muscle myopathy with impaired O_2 utilization as the cause of the limited peak $\dot{V}O_2$ and O_2 pulse. Had exercise capacity been limited by a defect in oxidative function of the skeletal muscle, O_2 extraction would have been less than normal and cardiac output would probably have been higher, rather than lower, than normal for a given $\dot{V}O_2$. Autonomic dysfunction with impaired distribution of blood flow to the exercising muscles, on the other hand, would be associated with normal O_2 extraction across the leg but low extraction across the circulation as a whole, so this too was excluded by the data.

The key finding in this case was thus the low stroke volume. The basis for this was not evident from the prior echocardiogram, which excluded systolic dysfunction or structural heart disease. Although diastolic dysfunction could account for the exercise response, he did not have recognized risk factors for this condition, nor any echocardiographic findings in support of it. A restrictive cardiomyopathy or pericardial process would also be compatible with the exercise responses but were not supported by data from the right heart catheterization (data not shown). Dynamic hyperinflation of the lungs resulting from obstructive airways disease can limit venous return and, therefore, cardiac stroke volume due to development of high intrathoracic pressures. This condition should be considered in light of the patient's obstructive lung disease but was thought unlikely to account for the low cardiac output at rest and early stages of exercise. It was speculated that the findings may reflect low cardiac preload, limiting diastolic filling of the heart, and, consequently, reduced cardiac output. This could result from an abnormally low blood volume and be exacerbated with exercise by peripheral vascular dilatation due to high-grade lactic acidosis. The low venous return would predispose to hypotension after exercise with a tachycardia, in contrast to the bradycardia that would characterize a vasovagal event. A condition of low venous return could account for the prominent symptom of syncope or near syncope with exercise.

Conclusion

This was a very challenging case. It is presented here as an illustration of one of the relatively uncommon instances in which measurement of cardiac output is critical for distinguishing between circulatory problems versus muscle disease as the cause of abnormalities in exercise $\dot{V}O_2$.

Table 10.33.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	3.28	1.69
Maximum heart rate (beats/min)	192	176
Maximum O_2 pulse (mL/beat)	17.2	9.8
$\Delta\dot{V}O_2/\Delta WR$, (mL/min/W)	10.3	7.9
AT (L/min)	<1.41	0.90
Blood pressure (mm Hg [rest, max])		155/85, 160/90
Maximum $\dot{V}E$, (L/min)		90
Exercise breathing reserve (L/min)	>15	20
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	23.6	32.6
PaO_2 (mm Hg [rest, max ex])		86, 105
$P(A-a)O_2$ (mm Hg [rest, max ex])		11, 17
$PaCO_2$ (mm Hg [rest, max ex])		41, 38
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		4, 7
VD/VT (rest, sub max, max ex)		0.47, 0.31, 0.41
HCO_3^-, (mEq/L [rest, recovery])		26, 17
Lactate (mEq/L [recovery])		13.7

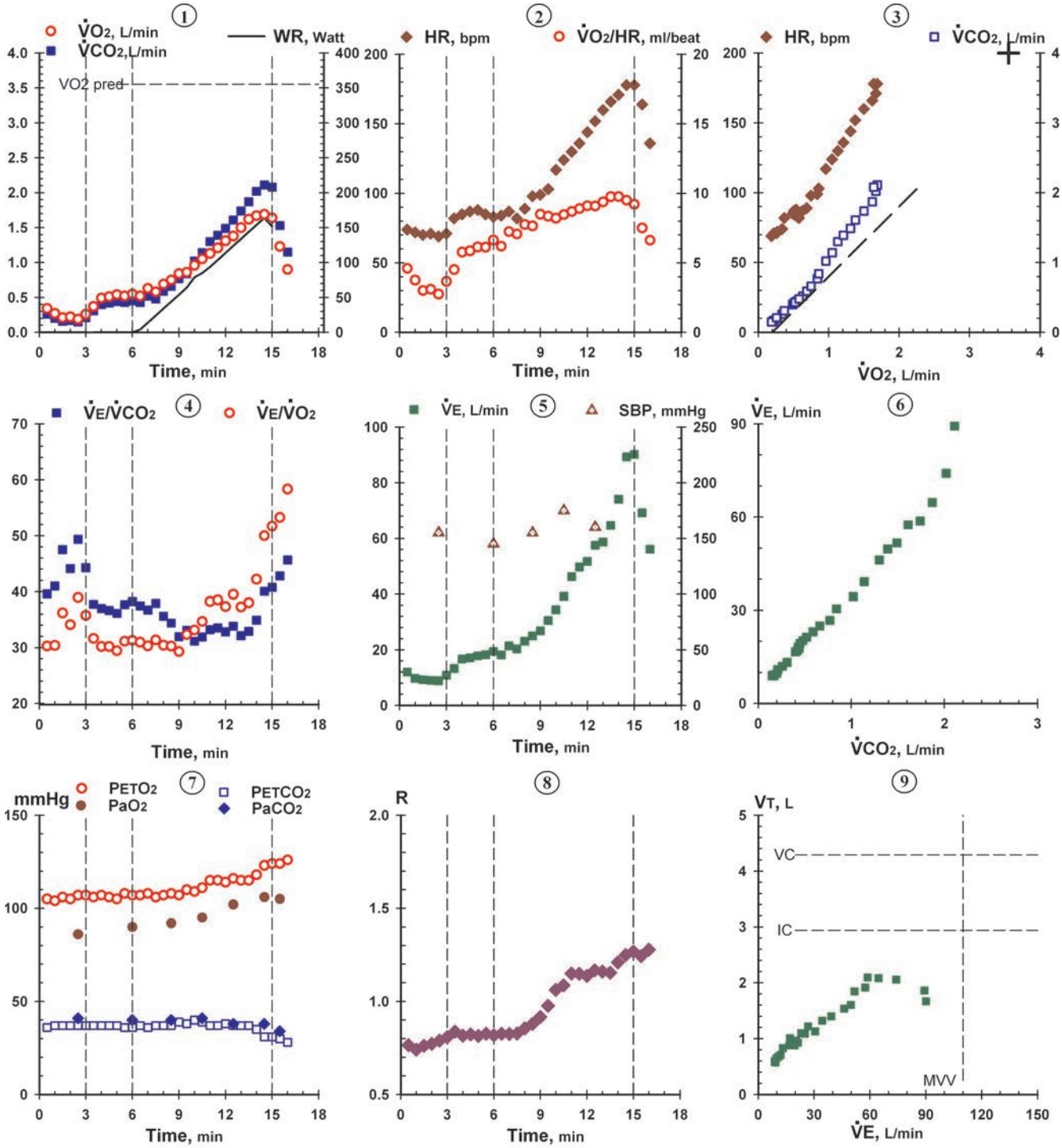

FIGURE 10.33.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.33.3

Air breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0																				
0.5	Rest		74	17	12.0	0.26	0.34	4.6	0.76			105			36			39	30	
1.0	Rest		72	15	9.7	0.20	0.27	3.8	0.74			104			37			41	30	
1.5	Rest		70	16	9.2	0.16	0.21	3.0	0.76			106			37			47	36	
2.0	Rest		71	15	9.0	0.17	0.22	3.1	0.77			105			37			44	34	
2.5	Rest	155/85	69	15	8.9	0.15	0.19	2.8	0.79	7.40	25	107	86	14	37	41	4	49	39	0.47
3.0	Rest		71	16	10.9	0.21	0.26	3.7	0.81			107			37			44	35	
3.5	Unloaded		82	16	13.3	0.31	0.37	4.5	0.84			106			37			37	31	
4.0	Unloaded		85	19	16.7	0.40	0.49	5.8	0.82			107			37			37	30	
4.5	Unloaded		87	17	17.1	0.42	0.51	5.9	0.82			106			37			36	30	
5.0	Unloaded		88	19	17.8	0.44	0.54	6.1	0.81			105			37			36	29	
5.5	Unloaded		85	20	18.2	0.43	0.52	6.1	0.83			108			36			37	31	
6.0	Unloaded	145/85	83	22	19.4	0.45	0.55	6.6	0.82	7.41	25	107	90	13	36	40	4	38	31	0.38
6.5	4		84	20	18.1	0.43	0.52	6.2	0.83			107			37			37	31	
7.0	14		87	23	21.4	0.52	0.63	7.2	0.83			108			36			37	30	
7.5	24		82	21	20.3	0.48	0.58	7.1	0.83			106			37			38	31	
8.0	34		89	21	23.1	0.59	0.69	7.8	0.86			107			37			35	30	
8.5	44	155/85	98	23	25.0	0.66	0.75	7.7	0.88	7.40	24	108	92	14	37	40	3	34	30	0.33
9.0	54		99	22	26.8	0.77	0.84	8.5	0.92			107			39			32	29	
9.5	64		103	27	30.5	0.84	0.86	8.3	0.98			110			38			33	32	
10.0	79		117	26	34.4	1.02	0.96	8.2	1.06			109			40			31	33	
10.5	85	175/90	124	28	39.2	1.14	1.05	8.5	1.09	7.38	24	111	95	17	39	41	2	32	35	0.31
11.0	94		130	30	46.2	1.30	1.13	8.7	1.15			115			37			33	38	
11.5	104		136	31	49.7	1.39	1.21	8.9	1.15			115			37			33	38	
12.0	114		144	28	51.7	1.49	1.31	9.1	1.14			114			38			33	37	
12.5	124	160/90	152	30	57.5	1.61	1.38	9.1	1.17	7.39	23	116	102	14	37	38	1	34	39	0.31
13.0	134		160	28	58.7	1.74	1.50	9.4	1.16			115			37			32	37	
13.5	144		166	31	64.7	1.87	1.62	9.8	1.15			115			37			33	38	
14.0	154		171	36	74.1	2.02	1.67	9.8	1.21			118			35			35	42	
14.5	164		178	48	89.3	2.11	1.69	9.5	1.25	7.35	21	123	106	12	31	38	7	40	50	0.41
15.0	152		178	54	90.2	2.08	1.64	9.2	1.27			124			31			41	52	
15.5	Recovery		164	37	69.2	1.53	1.23	7.5	1.24	7.32	17	124	105	16	30	34	4	43	53	0.38
16.0	Recovery		136	36	56.1	1.15	0.90	6.6	1.28			126			28			45	58	

Table 10.33.4

Hemodynamic Responses to Exercise

			Systemic Artery			Pulmonary Artery			Femoral Vein					
Status	$\dot{V}_{O_2}$ (mL/min)	Heart rate (bpm)	O_2 cont (mL/100 mL)	PO_2 (mm Hg)	O_2 sat (%)	O_2 cont (mL/100 mL)	PO_2 (mm Hg)	O_2 sat (%)	O_2 cont (mL/100 mL)	PO_2 (mm Hg)	O_2 sat (%)	C (a − $\bar{v}$)o_2 (mL/100 mL)	S.V. (mL)	C.O. (L/min)
Rest	250	71	20.0	86	97	12.1	33	60	6.0	20	32	7.9	44	3.1
0 load	520	83	21.0	90	97	8.7	26	47	5.0	18	25	12.3	51	4.2
44 W	720	98	21.0	92	97	8.6	26	44	4.9	18	25	12.4	59	5.8
85 W	1000	124	21.0	95	97	8.2	25	39	5.8	21	29	12.8	63	7.8
124 W	1340	152	21.5	102	97	7.9	25	37	7.4	26	35	13.6	65	9.8
164 W	1680	176	22.0	106	97	6.1	23	29	6.7	25	31	15.9	60	10
(Max ex)	1640	164	22.0	105	97	4.8	20	22	5.1	23	24	17.2	58	9.5
6 min rec			21.0	99	97	14.5	45	69	17.0	55	80	6.5		

Case 34 Early Onset of Exercise Lactic Acidosis Suggesting Circulatory Impairment

CLINICAL FINDINGS

This 26-year-old man was referred for exercise testing after approximately 6 years of progressive exercise intolerance. He was active in competitive sports through high school and continued with recreational sports in college, but at some point noted that he was becoming unable to keep up with his peers. This progressed to feeling fatigued, lightheaded, near syncopal, and sometimes nauseated during or after vigorous exercise. He progressively scaled back his exercise activities to avoid these symptoms. At the time of referral he had already undergone a number of diagnostic evaluations including tilt table test and Holter monitoring, which were normal, and an echocardiogram with normal findings except for mild mitral prolapse without mitral regurgitation. A cardiopulmonary exercise test by his referring physician had been interpreted as showing a borderline *AT* but normal peak $\dot{V}O_2$ and did not reproduce his symptoms. A muscle biopsy was reported to show normal histology and normal concentrations of key enzymes involved in oxidative metabolism. He was referred for repeat exercise testing to further characterize his problem and determine if his functional capacity was changing. His medical history was notable only for Lyme disease, which was treated 3 years previously. Physical examination was unremarkable and the resting ECG was normal.

EXERCISE FINDINGS

This patient represented an unusual diagnostic challenge and underwent a number of exercise tests over a period of several years. One test will be presented in detail and selected data from others are presented in tabular form for comparison. At the time of his initial referral to our laboratory, exercise testing was conducted without blood sampling and showed that *AT* was reduced and peak $\dot{V}O_2$ and O_2 pulse were low normal or mildly reduced. All of these measures were lower than on a test performed 2 years earlier by the referring physician. This suggested progression of his impairment and raised the question of whether it was a circulatory or metabolic problem. Repeat testing was therefore planned with sampling of arterial, mixed venous, and femoral venous blood for hemodynamic assessment. Results of the latter test are presented here.

Femoral venous (directed caudally), brachial artery, and pulmonary artery catheters were placed prior to exercise. Exercise testing was conducted on a cycle ergometer starting with 3 minutes of unloaded cycling, followed by a progressive increase in work rate by 25 W per minute. The patient stopped exercise with symptoms of lightheadedness and was noted to be pale in the post-exercise period. He denied chest pain or symptoms of leg pain or fatigue. The brachial artery tracing demonstrated marked respiratory variation in blood pressure constituting a pulsus paradoxus of 40 to 50 mm Hg at peak exercise (150/110/70 mm Hg). At the end of exercise, systolic pressure dropped immediately to 98/70/50 and slowly recovered to 110/67 after 2 minutes of recovery. During this time, heart rate declined only from a peak of 190 to 140 bpm; there was no ectopy.

INTERPRETATION

Comments

Pulmonary function tests were essentially normal (Table 10.34.1).

Analysis

Peak $\dot{V}O_2$ was within the normal range (Table 10.34.2), though below the average predicted value and lower than what had been reported 2 years earlier by his referring physician. The striking finding on this test was that the anaerobic threshold was lower than predicted and was a relatively low percentage of the patient's peak $\dot{V}O_2$.

Table 10.34.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		26
Sex		Male
Height (cm)		180
Weight (kg)		78
Hemoglobin (g/dL)		16.4
VC (L)	5.69	6.06
IC (L)	3.80	4.48
FEV_1 (L)	4.75	5.05
FEV_1/VC (%)	83	83
MVV (L/min)	188	188
DLCO (mL/mm Hg/min)[a]	36.9	37.1

[a]Measured on a separate occasion.

Table 10.34.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	3.27	2.80
Maximum heart rate (beats/min)	194	192
Maximum O_2 pulse (mL/beat)	16.9	14.6
$\Delta\dot{V}O_2/\Delta WR$, (mL/min/W)	10.3	9.0
AT (L/min)	>1.4	1.1
Blood pressure (mm Hg [rest, max])		100/70, 158/80
Maximum $\dot{V}E$, (L/min)		161
Exercise breathing reserve (L/min)	>15	27
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	24.2	26.1
PaO_2 (mm Hg [rest, max ex])		89, 112
$P(A-a)O_2$ (mm Hg [rest, max ex])		8, 9
$PaCO_2$ (mm Hg [rest, max ex])		43, 34
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		5, –3
VD/VT (rest, sub max, max ex)		0.47, 0.14
HCO_3^-, (mEq/L [rest, recovery])		27, 16

Indices of pulmonary gas exchange were normal and the hemoglobin was high normal, so the finding of a low *AT* suggests either a circulatory or metabolic problem. Exercise gas exchange data are shown in Table 10.34.3 and Figure 10.34.1, and hemodynamic data are shown in Table 10.34.4. At peak exercise, O_2 extraction across the leg was normal (74%) and was also normal across the entire systemic circulation (70%). The functions of distribution of cardiac output to the working legs and extraction of O_2 by the muscle thus appeared intact. Cardiac output measures were obtained at rest by thermodilution and at two points during exercise by the Fick method, with the highest value of 16.6 L per minute measured at approximately 2 minutes prior to the end of exercise. From these measures, the slope of the increase in cardiac output was less than 4 L per minute for each liter per minute increase in $\dot{V}O_2$, which is probably lower than normal (5 to 6 L per minute per liter per minute $\dot{V}O_2$). So, in this case, as in the preceding Case 33 of this chapter, the cause of exercise intolerance appeared to be an inadequate increase in cardiac output despite imaging studies showing normal cardiac structure and function. In this case, the effect of limited blood flow was offset in part by a mild erythrocytosis, which increased the potential $C(a-\bar{v})O_2$ such that peak $\dot{V}O_2$ was within the normal range.

Over the following year, the patient continued to have reduced exercise tolerance and near-syncope with exertion, and so returned for further evaluation. To test the possibility that the circulatory problem was due to relative intravascular volume deficit, he underwent a pair of exercise tests, the first performed as a baseline, and the second the following day after intravenous volume loading with 750 mL of lactated Ringers solution and 150 mL of 25% albumin. Volume loading was associated with improved peak $\dot{V}O_2$ and *AT* (see Table 10.34.4) without significant difference in peak heart rate. No hematologic or endocrine basis for relative volume depletion was identified.

Conclusion

This perplexing patient had a near-normal peak exercise capacity but had exertional lightheadedness (near syncope), fatigue, and nausea. The findings of pulsus paradox during exercise and postexercise hypotension supported the impression that these symptoms might result from reduced cardiac output due to inadequate preload. Hemodynamic studies confirmed a marginally reduced cardiac output response to exercise, and an empiric challenge with intravenous loading was associated with acute improvement in exercise performance. The underlying cause of this condition was not clear.

Table 10.34.3

Air Breathing

Time (min)	Work rate (W)	BP (mmHg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mmHg ET	P_{O_2}, mmHg a	P_{O_2}, mmHg (A − a)	P_{CO_2}, mmHg ET	P_{CO_2}, mmHg a	P_{CO_2}, mmHg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0																				
0.5	Rest		86	17	10.0	0.20	0.25	2.9	0.80			102			38			40	50	
1.0	Rest	100/70	88	17	10.0	0.17	0.23	2.6	0.74			101			39			43	59	
1.5	Rest		85	14	7.8	0.13	0.18	2.1	0.74			100			40			43	59	
2.0	Rest	94/70	88	16	10.9	0.22	0.30	3.4	0.74			102			39			36	49	
2.5	Rest		90	13	11.2	0.20	0.30	3.3	0.65	7.40	27	107	89	8	38	43	5.0	37	57	0.47
3.0	Rest	108/62	99	18	15.7	0.40	0.52	5.3	0.76			101			40			30	39	
3.5	Unloaded		102	18	14.2	0.34	0.46	4.5	0.75			100			40			31	41	
4.0	Unloaded		102	19	17.2	0.48	0.61	6.0	0.79			102			40			28	36	
4.5	Unloaded	121/72	103	17	17.9	0.54	0.69	6.7	0.78	7.40	26	102	101	–3	40	42	1.0	26	33	0.30
5.0	Unloaded		102	18	19.9	0.55	0.67	6.6	0.83			105			39			30	36	
5.5	Unloaded		102	17	15.6	0.43	0.55	5.4	0.79			101			41			28	36	
6.0	Unloaded	111/69	103	14	18.4	0.56	0.69	6.7	0.81			103			40			27	33	
6.5	–2		102	15	17.9	0.55	0.68	6.7	0.81	7.41	27	103	105	–5	40	41	1.0	26	32	0.32
7.0	1		104	16	17.9	0.55	0.66	6.3	0.83			103			40			27	33	
7.5	7		104	18	18.5	0.48	0.58	5.6	0.83			101			41			32	39	
8.0	33	115/70	112	20	23.8	0.80	1.03	9.2	0.78			100			42			23	30	
8.5	41		110	17	25.0	0.79	0.97	8.9	0.81	7.38	26	103	91	6	41	45	3.0	26	32	0.31
9.0	64		114	18	23.1	0.82	0.95	8.3	0.87			102			43			24	28	
9.5	66		118	19	28.7	1.01	1.10	9.3	0.92			103			43			26	28	
10.0	75	123/68	124	18	28.8	1.03	1.12	9.0	0.92			103			44			26	28	
10.5	94		131	19	33.1	1.22	1.24	9.5	0.98	7.37	27	105	98	3	45	46	2.0	27	27	0.28
11.0	101		139	17	35.1	1.37	1.40	10.1	0.98			105			46			25	26	
11.5	116		143	19	39.1	1.53	1.47	10.3	1.04			105			46			27	26	
12.0	132	134/98	149	20	44.2	1.72	1.55	10.4	1.11			108			45			29	26	
12.5	139		155	17	47.7	1.91	1.73	11.2	1.10	7.36	25	107	100	10	45	43	–1.0	28	25	0.21
13.0	156		162	16	55.7	2.17	1.90	11.7	1.14			110			44			29	26	
13.5	168		166	17	56.1	2.17	1.91	11.5	1.14			109			44			29	26	
14.0	183	158/74	171	18	64.3	2.42	2.10	12.3	1.15			111			43			31	27	
14.5	191		177	19	74.5	2.72	2.26	12.8	1.20	7.34	23	114	100	15	41	40	–2.0	33	27	0.19
15.0	203		181	21	80.5	2.84	2.32	12.8	1.22			116			40			35	28	
15.5	219		182	23	84.6	2.94	2.41	13.2	1.22			116			38			35	29	
16.0	231	148/70	188	23	93.0	3.19	2.55	13.6	1.25			118			38			36	29	
16.5	242		191	37	125.5	3.63	2.74	14.3	1.32	7.31	19	124	112	9	33	34	–3.0	46	35	0.14
17.0	251	158/80	192	52	161.0	3.71	2.80	14.6	1.33			130			26			58	43	
17.5	276		190	45	123.4	2.70	1.96	10.3	1.38			132			24			63	46	
18.0	Recovery		184	39	102.7	2.20	1.40	7.6	1.57			134			24			73	47	
18.5	Recovery	101/63	179	38	95.8	1.88	1.15	6.4	1.63			135			22			83	51	
19.0	Recovery		170	34	82.9	1.59	1.01	5.9	1.57			135			22			82	52	
19.5	Recovery		161	34	72.2	1.37	0.91	5.7	1.51	7.23	16	135	152	–17	22	21	0.0	79	53	0.21
20.0	Recovery		152	28	52.9	1.12	0.81	5.3	1.38			131			25			65	47	
20.5	Recovery		143	32	48.5	1.00	0.78	5.5	1.28			131			24			62	49	

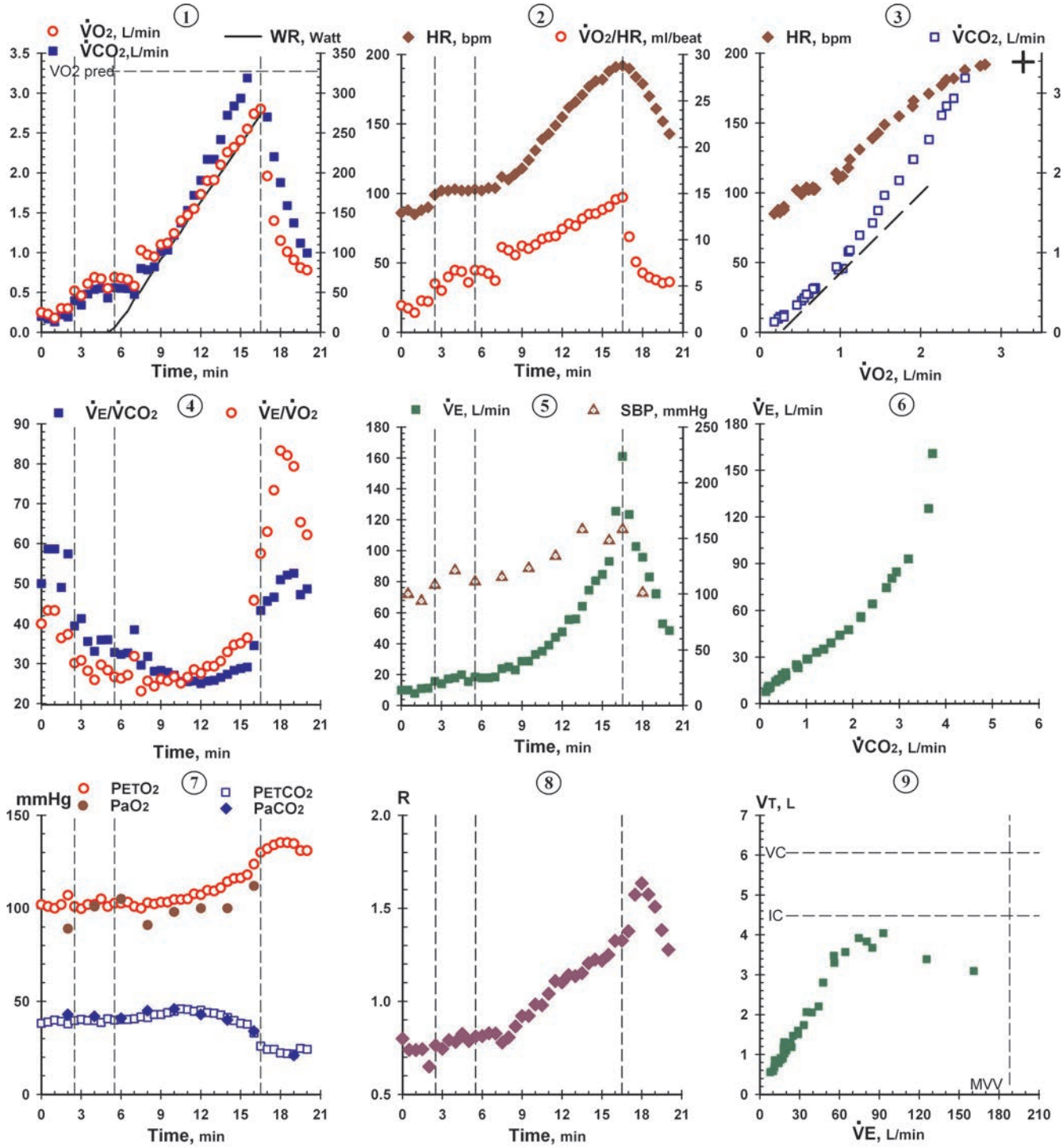

FIGURE 10.34.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 25 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.34.4

Selected Hemodynamic Variables

				Systemic		Leg	
Work rate (W)	$\dot{V}O_2$ (L/min)	Cardiac output (L/min)	Stroke volume (mL)	C (a – $\bar{v}$)O_2 (mL/dL)	O_2 extraction (%)	C (a – $\bar{v}$)O_2 (mL/dL)	O_2 extraction (%)
Rest (supine)	0.34	7.8	92	4.35	20	11.4	54
Unloaded	0.56					11.6	56
11	0.69					11.1	54
58	0.91					12.9	61
107	1.19	12.74	91	9.34	43	12.5	59
156	1.6					13.8	65
204	2.16					15.6	72
252	2.65	16.67	87	15.9	70	16.3	72
276	2.49					16.6	74
Recovery	0.97					5.9	27

Table 10.34.5

Selected Measures from Exercise Tests Conducted over 4 Years

Time relative to presented test	Peak $\dot{V}O_2$ (L/min)	*AT* (L/min)	Peak HR (bpm)	Peak O_2 pulse (mL/beat)	$\Delta\dot{V}O_2/\Delta WR$	[Hb], rest (g/dL)	Blood pressure (mm Hg)	
							Rest	Peak exercise
2 years earlier	3.57	1.37	192	18.6		17.2		
1 year earlier	2.66	1.3	193	13.8	8.6		127/81	156/86
1 day earlier	2.67	1.1	189	14.1	8.2		133/84	169/77
Present test	2.80	1.1	192	14.6	9.0	16.4	100/70	158/80
1 year later baseline	3.30	1.1	187	17.7	9.8	18.6	127/73	194/94
1 year later post-volume loading	3.73	1.4	185	20.5	10.7	16.5	113/70	167/56

Case 35 Pulmonary Hypertension with Patent Foramen Ovale

CLINICAL FINDINGS

This 61-year-old woman had first noted mild exertional dyspnea 3 years prior to evaluation. Sometime later, she began to have recurring episodes of depression and confusion. She was evaluated in emergency departments for acute episodes of dyspnea, chest pain, and anxiety, which were interpreted as panic anxiety attacks. She was given a benzodiazepam for her mental symptoms and a β-blocker for systemic hypertension. She subsequently presented to the psychiatric emergency department with acute anxiety and suicidal ideation. Medical evaluation revealed findings of pulmonary hypertension including increased pulmonary artery size on chest radiograph, right ventricular hypertrophy on ECG, and hypoxemia on arterial blood gas analysis. With oxygen therapy, her mental status improved. There was no history of cigarette smoking, exposure to environmental toxins, pulmonary emboli, or thrombophlebitis. Exercise testing was requested to evaluate her functional status and the mechanism of her hypoxemia. Examination at the time revealed mild obesity, hypertension, and a prominent S_4 heart sound.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. She pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 5 W per minute to her symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. She stopped exercise because of shortness of breath. There were no arrhythmias, ST-segment changes, or T-wave changes with exercise. Following a rest period of 30 minutes, the exercise study was repeated with the patient breathing 100% oxygen.

INTERPRETATION

Comments

The results of this patient's resting respiratory function tests showed mild airway obstruction (Table 10.35.1). The ECG was compatible with right ventricular hypertrophy. The exercise test was repeated with the subject breathing 100% oxygen to evaluate the possible development of a right-to-left shunt through a foramen ovale when exercise-induced right atrial pressure rose due to increased venous return—a possible cause of activity-induced hypoxemia, which might contribute to this patient's symptoms.

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ was reduced and the anaerobic threshold was indeterminate but probably low (Table 10.35.2). Referring to Flowchart 4 (Fig. 8.4), the breathing reserve was normal (branch point 4.1). The $\dot{V}E/\dot{V}CO_2$ during exercise was high (branch point 4.3), supporting the diagnosis of abnormal pulmonary circulation. The patient was hyperventilating with a very high $\dot{V}E/\dot{V}CO_2$. However, based on the gas exchange ratio of 0.8 at rest and exercise, the reduced $PaCO_2$ was chronic. Furthermore, the VD/VT calculated using the arterial PCO_2 was increased (Table 10.35.3), confirming that the elevated ventilatory response to exercise was due to elevated dead space, rather than hyperventilation alone. Branch point 4.5 further distinguishes between abnormal pulmonary circulation due to moderate-to-severe left ventricular failure and that due to pulmonary vascular disease, in that the patient became very hypoxemic with exercise. These findings are supportive of the diagnosis of primary pulmonary vascular disease.

Table 10.35.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		61
Sex		Female
Height (cm)		147
Weight (kg)	53	61
Hematocrit (%)		37
VC (L)	2.33	2.31
IC (L)	1.56	1.59
TLC (L)	3.66	4.53
FEV_1 (L)	1.90	1.59
FEV_1/VC (%)	81	69
MVV (L/min)	73	59
DLCO (mL/mm Hg/min)	17.6	17.3

Table 10.35.2

Selected Exercise Data

Measurement	Predicted	Room air	Oxygen
Maximum work rate (W)		20	25
Peak $\dot{V}O_2$ (L/min)	1.23	0.62	
Maximum heart rate (beats/min)	159	87	85
Maximum O_2 pulse (mL/beat)	7.8	7.1	
AT (L/min)	>0.61	Indeterminate	
Blood pressure (mm Hg [rest, max])		186/90, 204/90	172/84, 210/102
Maximum $\dot{V}E$ (L/min)		38	42
Exercise breathing reserve (L/min)	>15	21	17
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	30.1	46.3	50.4
PaO_2 (mm Hg [rest, max ex])		71, 40	550, 70
$P(A-a)O_2$ (mm Hg [rest, max ex])		42, 79	138, 612
$PaCO_2$ (mm Hg [rest, max ex])		28, 31	25, 31
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		5, 12	4, 9
V_D/V_T (rest, heavy ex)		0.31, 0.47	0.34, 0.47
HCO_3^- (mEq/L [rest, 2-min recov])		22, 20	22, 18

Table 10.35.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	186/90								7.56	21		77			24				
0.5	Rest		60	16	6.8	0.11	0.14	2.3	0.79			122			23			49	39	
1.0	Rest		60	11	6.7	0.12	0.16	2.7	0.75			120			23			48	36	
1.5	Rest		59	17	8.8	0.15	0.22	3.7	0.68			119			24			49	33	
2.0	Rest	206/114	61	14	8.4	0.15	0.21	3.4	0.71	7.52	22	120	71	42	23	28	5	48	34	0.31
2.5	Unloaded		66	22	11.7	0.19	0.25	3.8	0.76			122			23			52	39	
3.0	Unloaded		67	17	11.2	0.20	0.27	4.0	0.74			121			23			49	36	
3.5	Unloaded		71	19	13.7	0.25	0.32	4.5	0.78			121			23			48	38	
4.0	Unloaded	191/94	73	23	14.9	0.27	0.35	4.8	0.77	7.50	21	121	58	57	23	28	5	48	37	0.31
4.5	5		74	32	15.0	0.27	0.37	5.0	0.73			115			27			45	33	
5.0	5		76	23	15.3	0.30	0.39	5.1	0.77			119			25			44	34	
5.5	10		79	26	23.6	0.45	0.58	7.3	0.78			116			26			48	37	
6.0	10	202/96	81	27	25.3	0.46	0.52	6.4	0.88	7.47	23	125	43	72	22	32	10	50	44	0.42
6.5	15		81	25	23.9	0.47	0.57	7.0	0.82			120			25			46	38	
7.0	15		84	32	26.6	0.47	0.54	6.4	0.87			124			23			51	44	
7.5	20		87	36	27.8	0.47	0.58	6.7	0.81			126			22			53	43	
8.0	20	204/90	87	35	37.7	0.61	0.62	7.1	0.98	7.45	21	130	40	79	19	31	12	57	56	0.47
8.5	Recovery		82	33	33.3	0.57	0.61	7.4	0.93			127			21			54	50	
9.0	Recovery		80	28	29.1	0.51	0.55	6.9	0.93			127			21			52	49	
9.5	Recovery		79	23	21.9	0.41	0.46	5.8	0.89			122			24			49	43	
10.0	Recovery	198/87	79	27	24.8	0.43	0.48	6.1	0.90	7.45	20	126	50	67	22	30	8	52	47	0.41

Table 10.35.4

Oxygen Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	171/78								7.50	21		67			28				
0.5	Rest		58	14	13.7	0.22									20			57		
1.0	Rest		58	16	9.9	0.14									20			61		
1.5	Rest		57	16	9.5	0.14									20			58		
2.0	Rest	172/84	58	15	9.3	0.14				7.53	21		550	138	21	25	4	57		0.34
2.5	Unloaded		67	25	12.6	0.18									21			58		
3.0	Unloaded		68	27	14.5	0.20									21			61		
3.5	Unloaded		66	26	14.3	0.23									22			53		
4.0	Unloaded	180/87	67	29	16.5	0.26				7.48	22		386	297	22	30	8	54		0.40
4.5	Unloaded		70	20	18.2	0.32									22			52		
5.0	Unloaded		70	23	17.5	0.31									23			50		
5.5	5		72	28	17.3	0.29									24			51		
6.0	5		73	26	18.3	0.32									25			50		
6.5	10		74	25	17.6	0.30									25			52		
7.0	10	180/84	77	26	24.2	0.42				7.44	22		100	580	23	33	10	52		0.45
7.5	15		80	29	28.5	0.48									22			54		
8.0	15		81	34	29.9	0.48									22			56		
8.5	20		82	31	29.0	0.50									22			53		
9.0	20	210/102	84	32	34.5	0.56				7.45	21		70	612	22	31	9	57		0.47
9.5	25		85	36	42.3	0.64									19			61		
10.0	Recovery		80	31	38.4	0.62									20			58		
10.5	Recovery		78	25	30.5	0.54									21			53		
11.0	Recovery		76	24	28.2	0.49									21			53		
11.5	Recovery	198/92	74	22	25.2	0.43									21			54		

At the lowest work rate, Pa_{O_2} abruptly decreased and continued to decrease as the work rate increased. Moreover, $P(a-ET)_{CO_2}$ continued to increase, and the V_D/V_T becomes progressively more abnormal as the work rate increased (Table 10.35.3). These changes in Pa_{O_2}, Pa_{CO_2}, and V_D/V_T suggest the development of a right-to-left shunt during exercise. There was also clear evidence of oxygen flow limitation in that $\dot{V}_{O_2}$ and O_2 pulse failed to increase with increasing work rate (Fig. 10.35.1, panels 1 and 2, respectively).

To verify whether a right-to-left shunt developed with exercise, Pa_{O_2} was measured at rest and during exercise while the patient was breathing 100% oxygen (Table 10.35.4). At rest, Pa_{O_2} was at the lower limits of normal (550 mm Hg); however, with mild exercise, it dropped to 70 mm Hg. This can only be explained by the development of a right-to-left shunt (in contrast, see Case 40 in this chapter in which exercise hypoxemia results from V:Q mismatching, which is fully reversed with oxygen breathing).

Subsequently, the patient underwent right heart catheterization. Pulmonary artery pressures were found to be at systemic pressure levels and the catheter slipped easily through a foramen ovale into the left atrium.

Conclusion

A diagnosis of pulmonary vascular occlusive disease with exercise-induced right-to-left shunt through a patent foramen ovale was made by the exercise studies, and was later confirmed by a right heart catheterization. Etiologies of secondary pulmonary vascular disease were excluded and she was diagnosed as having "primary," or idiopathic, pulmonary hypertension. We speculate that episodic anxiety may have been triggered by transient hypoxemia due to right-to-left shunting during exercise. Her depression and anxiety improved markedly once a physical basis for her symptoms was identified.

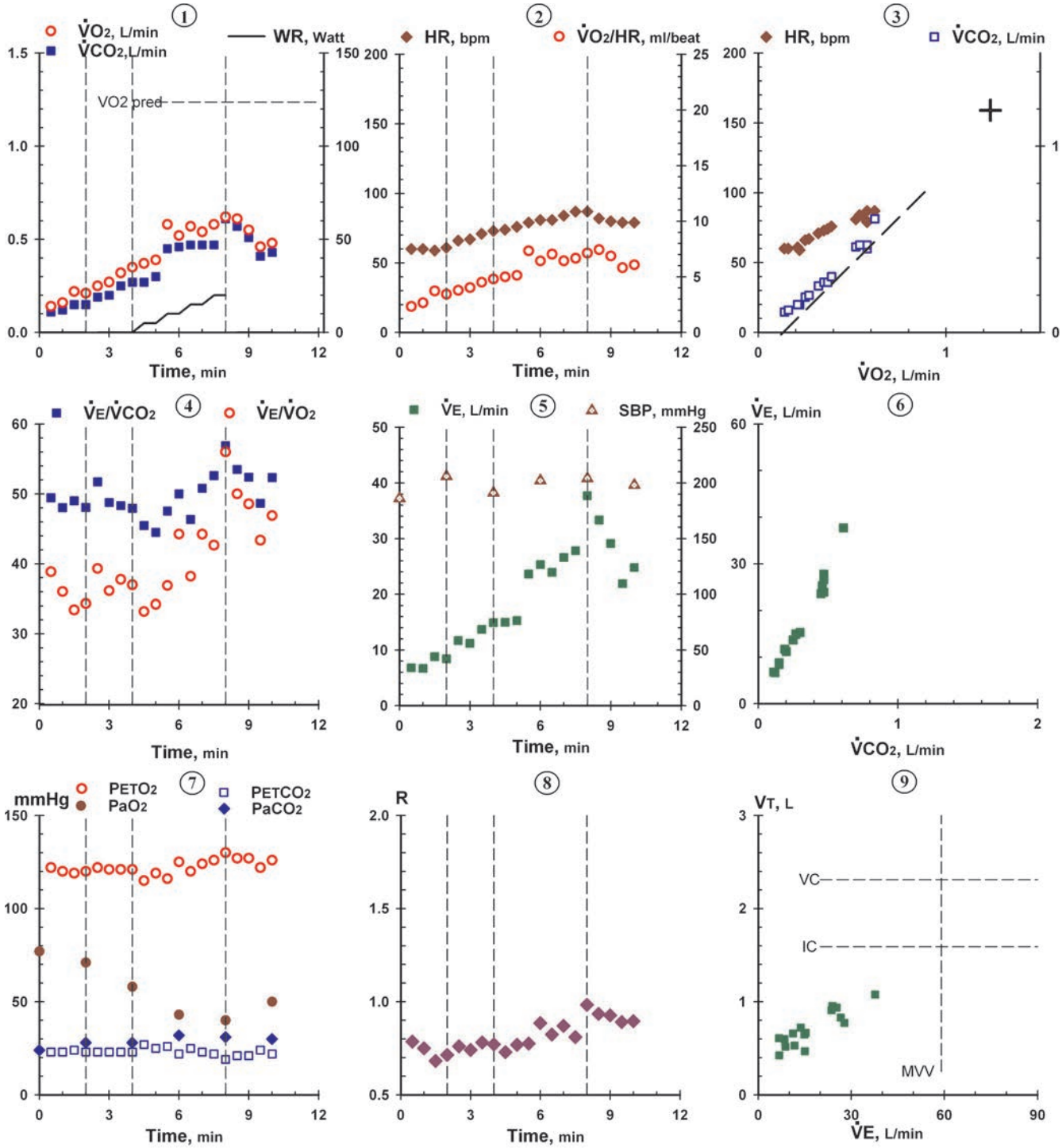

FIGURE 10.35.1. Air breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 5 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

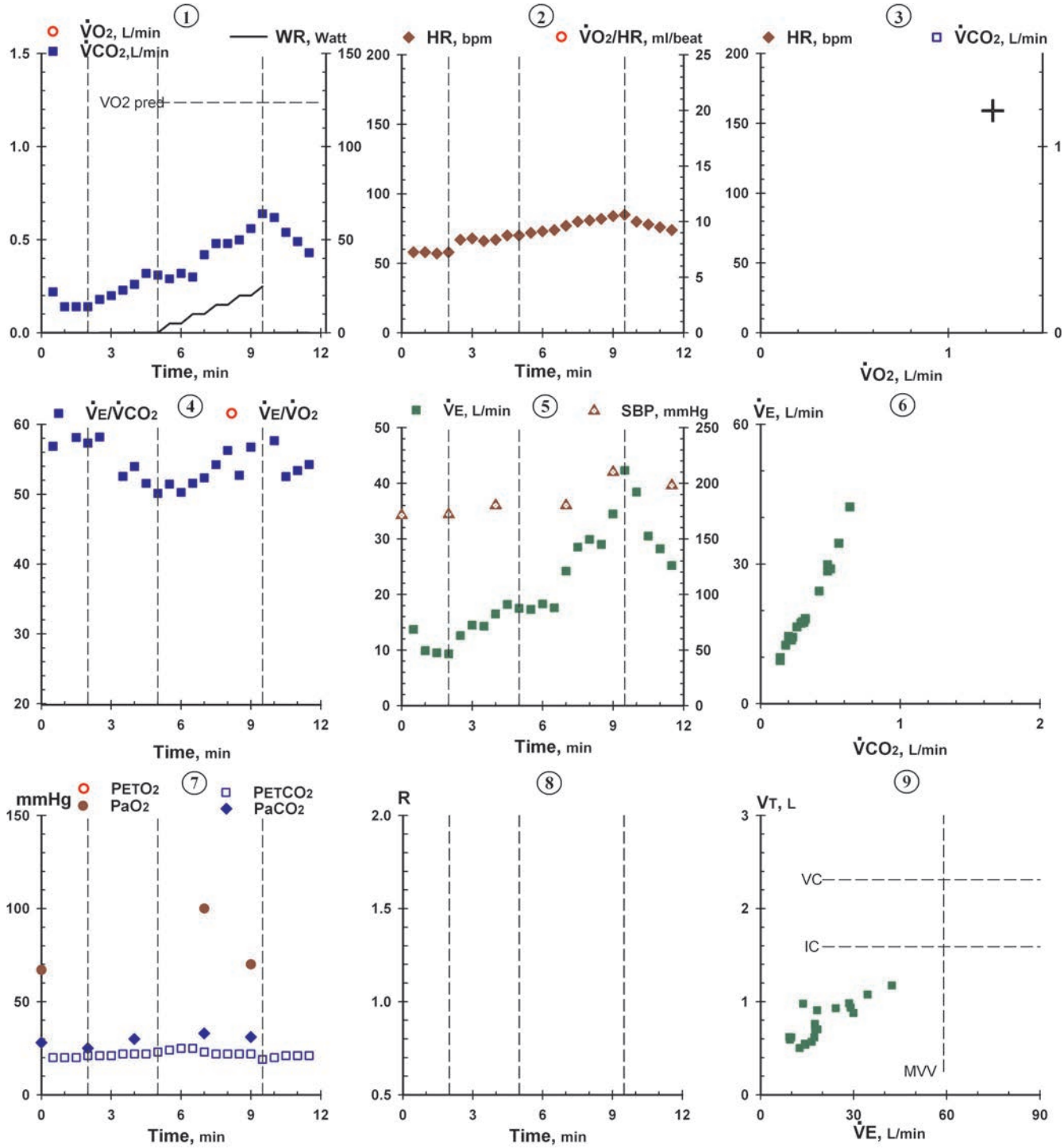

FIGURE 10.35.2. Oxygen breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 5 W per minute, and start of recovery. Oxygen uptake data are not shown because of technical limitations of calculation with very high-inspired oxygen levels.

Case 36 Idiopathic Pulmonary Hypertension before and after Treatment

CLINICAL FINDINGS

This 51-year-old woman was referred for cardiopulmonary exercise testing to evaluate the severity of her pulmonary hypertension. She had experienced progressive exertional dyspnea for 2 to 3 years prior to undergoing right heart catheterization with demonstration of pulmonary hypertension. Her history was notable for exposure to the appetite suppressants fenfluramine and phentermine (Fen-Phen) for a period of 7 months 5 years previously. Other causes of secondary pulmonary hypertension were excluded, and the diagnosis of pulmonary hypertension associated with anorexigen use was made. She also had systemic hypertension and was being treated with verapamil, benazepril, atorvastatin, and low-dose aspirin.

Two cardiopulmonary exercise tests of this patient are presented: The first was performed soon after pulmonary hypertension was diagnosed (see Fig. 10.36.1), and the second 6 weeks after starting treatment with an oral endothelin-1 receptor antagonist (see Fig. 10.36.2). The first test was done to characterize the severity of her disease and the range of her functional capacity and the second to obtain objective information on the effect of therapy on her exercise tolerance.

EXERCISE FINDINGS

On both occasions of testing, the patient performed exercise on a cycle ergometer. The protocol consisted of 3 minutes of rest and 3 minutes of unloaded cycling at 60 rpm, followed by a progressive increase in work rate of 10 W per minute until she reached symptom limitation due to shortness of breath. Twelve-lead ECG recordings were obtained during rest, every minute of exercise, and recovery. Arterial oxyhemoglobin saturation was continuously monitored with a pulse oximeter on her index finger. The patient performed the exercise tests with good effort.

INTERPRETATION

Comments

Resting pulmonary function was normal (Table 10.36.1). Her ECG showed right ventricular hypertrophy and strain pattern. Her exercise ECGs remained unchanged from rest except for rate.

Table 10.36.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		51
Sex		Female
Height (cm)		164
Weight (kg)		99
Hematocrit (%)		41
VC (L)	3.20	3.01
IC (L)	2.13	2.25
ERV (L)	1.07	0.76
FEV_1 (L)	2.63	2.53
FEV_1/VC (%)	82	84
MVV (L/min)	97	112
DLCO (mL/mm Hg/min)	22.7	25.7

Analysis

Referring to the baseline study (prior to treatment) in Tables 10.36.2 and 10.36.3, the accompanying nine-panel graphical array (Fig. 10.36.1), and the flowcharts, the findings lead to the diagnosis of pulmonary vascular disease. Her peak $\dot{V}O_2$ and *AT* were low, leading from Flowchart 1 (Fig. 8.1) to Flowchart 4 (Fig. 8.4). The breathing reserve was normal (branch point 4.1), and the ventilatory equivalent for $\dot{V}CO_2$ at the *AT* (branch point 4.3) was high, leading to the category of abnormal pulmonary circulation. The exercise oxyhemoglobin saturation was low (branch point 4.5), leading to the diagnosis of pulmonary vascular disease in contrast to the alternate diagnosis of left ventricular failure. She did not have direct arterial blood gas measurements. Therefore, the supportive information in items 2 through 4 of the confirmatory box were not available. However, other noninvasive measurements support the diagnosis of pulmonary hypertension. Beside the low peak $\dot{V}O_2$ and *AT* values, which are often the only measurements referred to in research studies of these patients, there are independent physiologic markers of impaired perfusion of ventilated lung characteristic of

Table 10.36.2

Selected Exercise Data

Measurement	Predicted	Baseline	After treatment
Peak $\dot{V}O_2$ (L/min)	1.70	0.86	0.93
Maximum heart rate (beats/min)	168	134	136
Maximum O_2 pulse (mL/beat)	10.0	6.4	6.8
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	7.3	8.7
AT (L/min)	>0.83	0.57	0.57
Blood pressure (mm Hg [rest, max])		131/89, 201/79	125/73, 165/96
Maximum $\dot{V}E$ (L/min)		51	45
Exercise breathing reserve (L/min)	>15	61	67
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.5	45.9	37.9
$PETCO_2$ @ *AT* (mm Hg)	<40	24	30
$\dot{V}E$ vs. $\dot{V}CO_2$ slope	<32	48	34
SaO_2 pulse oximeter (% [rest, max ex])	>95	96, 81	96, 93

Table 10.36.3

Baseline, Pretreatment

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{VD}{VT}$
												ET	*a*	(*A* − *a*)	*ET*	*a*	(*a* − *ET*)			
0.5	Rest		82	19	9.1	0.18	0.26	3.1	0.69			119			29			46	32	
1.0	Rest		82	23	11.7	0.22	0.32	3.9	0.69			111			39			47	33	
1.5	Rest		87	21	10.8	0.21	0.28	3.2	0.75			115			29			47	35	
2.0	Rest	132/91	86	19	8.9	0.17	0.25	2.8	0.70			111			29			46	32	
2.5	Rest		84	17	8.8	0.20	0.27	3.2	0.73			109			30			41	30	
3.0	Rest		86	18	8.7	0.18	0.26	3.0	0.69			109			30			44	30	
3.5	Unloaded		92	29	18.2	0.35	0.43	4.7	0.82			117			27			48	39	
4.0	Unloaded		99	31	20.7	0.38	0.42	4.2	0.92			123			25			50	46	
4.5	Unloaded		100	35	22.9	0.42	0.46	4.6	0.91			123			25			51	46	
5.0	Unloaded		101	34	22.1	0.41	0.46	4.6	0.89			122			25			50	44	
5.5	Unloaded		101	36	22.8	0.42	0.47	4.6	0.90			122			25			50	45	
6.0	Unloaded		102	37	24.3	0.44	0.48	4.7	0.92			124			24			51	47	
6.5	Unloaded		104	39	24.3	0.43	0.48	4.6	0.91			123			25			52	47	
7.0	Unloaded		103	36	23.6	0.43	0.49	4.7	0.89			122			25			50	45	
7.5	5		103	36	23.0	0.42	0.49	4.7	0.87			122			25			50	44	
8.0	10		106	37	24.6	0.46	0.52	4.9	0.88			122			25			50	44	
8.5	15		110	39	27.3	0.51	0.56	5.1	0.91			123			24			50	45	
9.0	20		114	37	29.2	0.55	0.59	5.1	0.93			123			24			50	47	
9.5	25		117	38	32.7	0.62	0.65	5.6	0.95			124			24			50	47	
10.0	30		121	36	24.9	0.67	0.68	5.6	0.99			125			23			34	34	
10.5	35		123	37	37.5	0.72	0.71	5.8	1.01			126			23			49	50	
11.0	40		124	36	32.6	0.76	0.77	6.2	0.99			125			24			40	40	
11.5	45		127	36	43.0	0.94	0.91	7.1	1.03			126			23			44	45	
11.5	50		130	31	44.3	0.88	0.83	6.4	1.05			126			23			49	51	
12.0	55		133	39	51.0	0.96	0.86	6.5	1.11			129			22			51	57	
12.5	60	214/106	134	37	46.9	0.89	0.80	6.0	1.11			122			22			51	56	
13.0	Recovery		125	34	42.5	0.84	0.80	6.4	1.06			126			23			49	51	
13.5	Recovery		113	29	31.0	0.68	0.69	6.1	0.98			122			27			44	43	
14.0	Recovery		108	29	26.6	0.58	0.58	5.4	1.01			121			29			43	44	
14.5	Recovery	169/960	105	31	24.3	0.52	0.49	4.7	1.06			122			28			44	46	

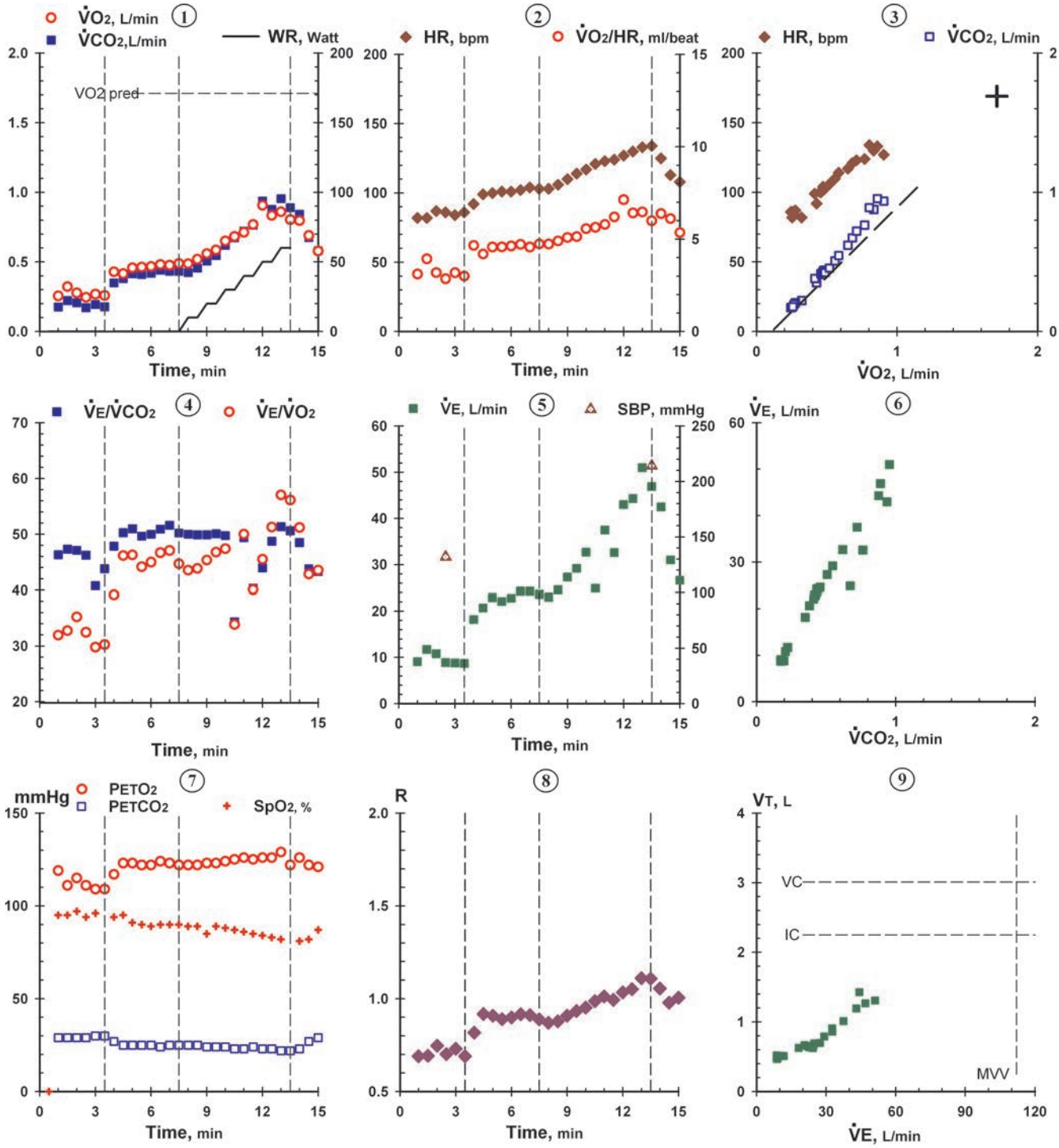

FIGURE 10.36.1. Before treatment. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

the pulmonary vasculopathy leading to pulmonary hypertension. These include the abnormally steep slope of $\dot{V}E$ versus $\dot{V}CO_2$ (Fig. 10.36.1, panel 6) and high $\dot{V}E/\dot{V}CO_2$ at the anaerobic threshold (Table 10.36.2 and Fig. 10.36.1, panel 4). The latter was 51 in this patient, with a normal value predicted between 25 and 32. This reflects failure to perfuse ventilated lung normally. In this case, the patient required approximately double the normal ventilation to perform a given level of exercise. Furthermore, arterial hypoxemia, particularly with a right-to-left shunt with exercise, is a feature of primary pulmonary hypertension, not left ventricular failure.

An additional important abnormality is evident in the study shown in the first test in Figure 10.36.1. At the start of exercise (minute 3), $PETCO_2$ abruptly decreases and $PETO_2$ abruptly increases (panel 7), with similar increases in R (panel 8), $\dot{V}E/\dot{V}O_2$, and $\dot{V}E/\dot{V}CO_2$ (panel 4). These directional changes are the opposite of normal and are characteristic of the opening of a right-to-left shunt through a foramen ovale at the start of exercise, as described by Sun et al.[1] The mechanism can be attributed to the sudden increase in venous return and right atrial filling at the start of exercise causing right atrial pressure to exceed left atrial pressure, with some of the venous return shunting through the foramen ovale and causing arterial desaturation (panel 7). This causes humoral ventilatory stimuli (decreased PaO_2 and increased $PaCO_2$ and H^+), to reach arterial chemoreceptors, acutely driving ventilation higher than would be predicted from the ventilation–perfusion mismatching caused by the underlying pulmonary vasculopathy. (In comparison, these changes were not as clearly identified in the noninvasive measurements of the patient described in Case 35 of this chapter. In that case, an exercise-induced shunt was clearly demonstrated, but the acute changes in end-tidal gas tensions, R, and ventilatory equivalents were obscured by preexisting hyperventilation.)

This woman underwent repeat testing after 6 weeks of treatment at which time she reported considerable symptomatic improvement. The posttreatment study is compared with the pretreatment study in Table 10.36.2 and Figures 10.36.1 and 10.36.2. The peak $\dot{V}O_2$ was modestly improved, and the *AT* was unchanged. The major improvement is evident in the reduction in the arterial desaturation during exercise (SpO_2 of 93% as compared with 81% at the end of exercise). This implies less right atrial pressure increase at the start of exercise and lesser intra-atrial shunting. This is supported by decrease, rather than increase, in the $\dot{V}E/\dot{V}CO_2$ ratio, and stable, rather than decreased, $PETCO_2$ at the start of exercise. The overall improvement in the matching of perfusion to ventilation is reflected in the reduction in $\dot{V}E/\dot{V}CO_2$ and increase in $PETCO_2$ at the *AT* after treatment as compared with before treatment (39 as compared to 52 and 30 compared with 24, respectively; Table 10.36.4).

Conclusion

This 51-year-old woman was symptomatic for several years prior to diagnosis of pulmonary hypertension. Her exercise gas exchange was characteristic of pulmonary vascular disease and also showed typical findings associated with an exercise-induced right-to-left shunt. Aerobic function improved modestly during treatment with an endothelin-1 receptor antagonist, but the stronger correlate to her reduction in symptoms of exertional dyspnea was a decrease in right-to-left shunt, which reduced ventilatory requirements during exercise substantially. Without the exercise data, this aspect of the patient's pathophysiology could not be fully appreciated.

REFERENCE

1. Sun XG, Hansen JE, Oudiz RJ, et al. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. *Circulation* 2002;105:54–60.

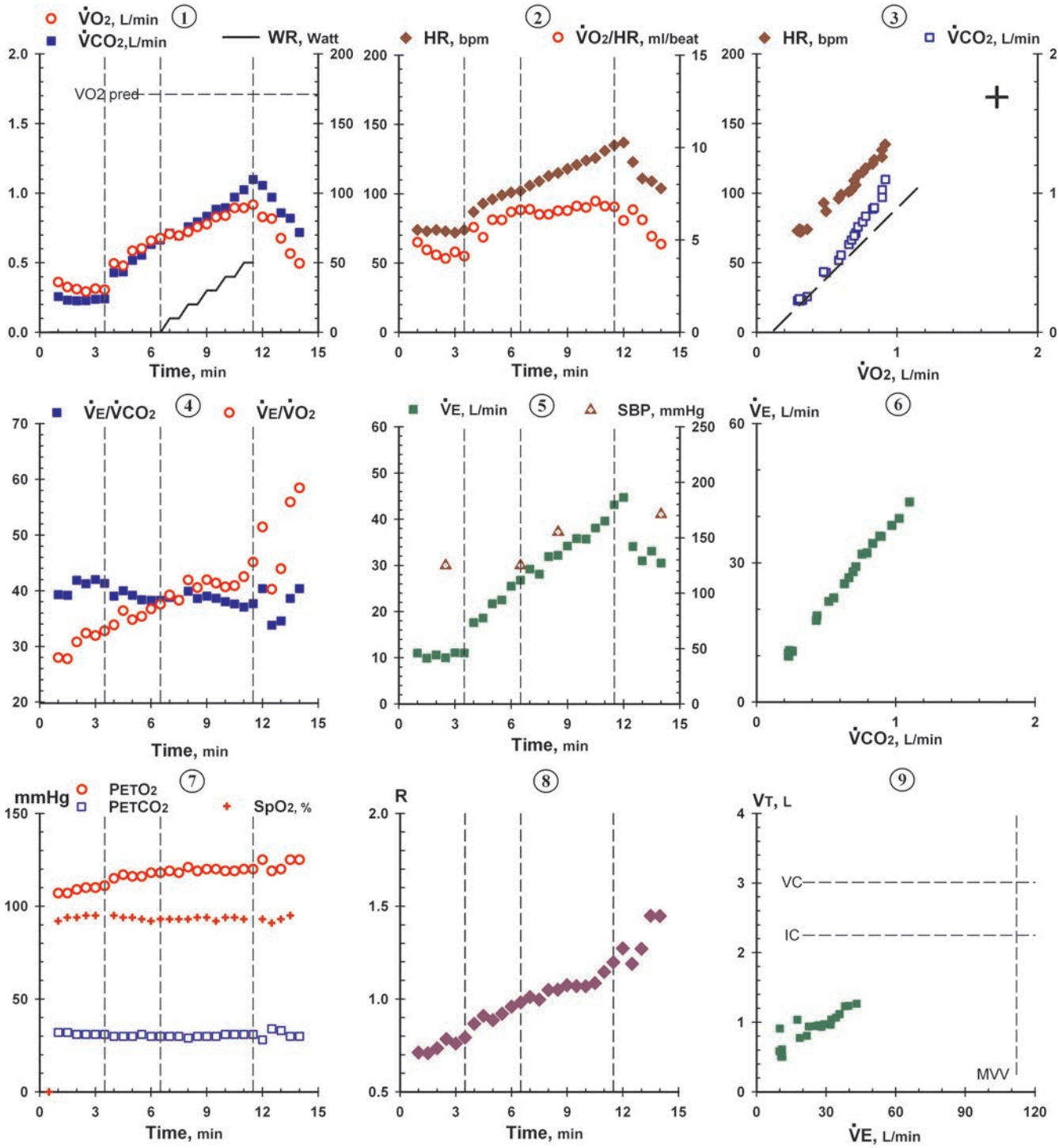

FIGURE 10.36.2. After 6 weeks of treatment. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.36.4

Posttreatment

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest		74	18	11.0	0.26	0.36	4.9	0.71			107			32			39	28	
1.0	Rest		73	17	9.9	0.23	0.33	4.5	0.71			107			32			39	28	
1.5	Rest		74	21	10.6	0.23	0.31	4.2	0.74			109			31			42	31	
2.0	Rest	125/73	73	11	10.0	0.23	0.29	4.0	0.78			110			31			41	32	
2.5	Rest		72	22	11.1	0.24	0.31	4.3	0.76			110			31			42	32	
3.0	Rest		74	20	11.0	0.24	0.31	4.1	0.79			111			31			41	33	
3.5	Unloaded		87	17	17.6	0.43	0.50	5.7	0.87			115			30			39	34	
4.0	Unloaded		93	24	18.6	0.44	0.48	5.1	0.91			117			30			40	36	
4.5	Unloaded		96	27	21.7	0.52	0.59	6.1	0.89			116			30			39	35	
5.0	Unloaded		99	24	22.5	0.56	0.60	6.1	0.92			116			31			38	35	
5.5	Unloaded		101	27	25.5	0.63	0.66	6.5	0.96			118			30			38	37	
6.0	Unloaded	125/58	102	28	26.8	0.66	0.68	6.6	0.98			118			30			38	38	
6.5	10		106	30	29.2	0.71	0.71	6.7	1.01			119			30			39	39	
7.0	10		109	30	28.1	0.69	0.70	6.4	1.00			118			30			38	38	
7.5	20		113	33	31.9	0.76	0.72	6.4	1.05			121			29			40	42	
8.0	20	155/90	115	31	32.2	0.79	0.76	6.6	1.05			119			30			39	41	
8.5	30		118	32	34.2	0.84	0.78	6.6	1.07			120			30			39	42	
9.0	30		121	32	35.8	0.89	0.83	6.8	1.07			120			30			39	41	
9.5	40		124	32	35.7	0.90	0.84	6.8	1.07			119			31			38	41	
10.0	40		126	31	38.1	0.97	0.89	7.1	1.09			119			31			38	41	
10.5	50		131	32	39.6	1.03	0.89	6.8	1.15			120			31			37	43	
11.0	50		135	34	43.1	1.10	0.92	6.8	1.20			120			31			38	45	
11.5	Recovery		137	41	44.7	1.06	0.83	6.1	1.27			125			28			40	51	
11.5	Recovery		123	25	34.1	0.97	0.82	6.6	1.19			119			34			34	40	
12.0	Recovery		111	26	31.0	0.86	0.68	6.1	1.27			120			33			35	44	
12.5	Recovery		109	29	33.1	0.82	0.57	5.2	1.45			125			30			39	56	
13.0	Recovery	171/82	104	30	30.5	0.72	0.50	4.8	1.45			125			30			40	58	

Case 37 Long-standing Idiopathic Pulmonary Hypertension: Serial Tests over 17 Years of Treatment

CLINICAL FINDINGS

At age 34, this man was found to have idiopathic pulmonary hypertension and was treated with a calcium channel blocker. His condition deteriorated such that, by age 38, he was disabled from his work and placed on a waiting list for heart–lung transplant. At age 40, pulmonary artery pressures were at systemic levels, and he was largely nonambulatory with signs and symptoms of right heart failure. With initiation of intravenous epoprostenol therapy, he had gradual improvement and progressively resumed activities. He first underwent exercise testing as part of a research protocol at age 41 soon after beginning epoprostenol. At age 47, he began to have annual exercise tests to track his functional capacity and response to changes in medications. Exercise tests performed at age 50 and at age 58 are presented here. At the time of both of these tests, he reported being physically active and doing construction projects around his home and property. He frequently experienced symptoms of lightheadedness but did not have syncope and identified fatigue and dyspnea as his major limiting symptoms. At age 50, his medications included intravenous epoprostenol, diuretics, warfarin, and digoxin. At the time of the test at age 58, epoprostenol had been replaced with subcutaneous treprostinil and oral sildenafil, and he was using supplemental oxygen at night. On both occasions, he was noted to have a flushed appearance, consistent with his prostacyclin therapy. Cardiac examinations were notable for a prominent second heart sound; there was minimal ankle edema. The resting ECG showed right ventricular hypertrophy.

EXERCISE FINDINGS

Both tests were conducted on a cycle ergometer, beginning after a period of rest with 3 minutes of pedaling at 60 rpm without added load, followed by continuous increase in work rate until the patient reached symptom limitation. On the first test, work rate was incremented by 10 W per minute, and on the subsequent test the increment was 15 W per minute. He ended both tests with leg fatigue. There were no significant ischemic changes on ECG during either test. Occasional ventricular ectopy was noted during the latter part of the second test.

INTERPRETATION

Comments

Pulmonary function tests showed low normal vital capacity and mild airflow obstruction with a reduction in DLCO at age 50. Airflow obstruction was of moderate severity at age 58 (Table 10.37.1).

Table 10.37.1

Selected Respiratory Function Data

	Age 50		Age 58	
Measurement	**Predicted**	**Measured**	**Predicted**	**Measured**
Age (years)		50		58
Sex		Male		Male
Height (cm)		183		183
Weight (kg)		88		90
VC (L)	5.16	4.59	5.17	3.83
IC (L)	3.44	3.46	3.53	3.27
FEV_1 (L)	4.19	3.02	3.93	2.12
FEV_1/VC (%)	81	66	76	55
MVV (L/min)	160	123	150	103
DLCO (mL/mm Hg/min)	31.6	23.8		

Analysis

On the first test shown at age 50, peak $\dot{V}O_2$ was moderately reduced relative to predicted values, and the *AT* was low (Table 10.37.2). However, $\Delta\dot{V}O_2/\Delta WR$ was normal, and O_2 pulse was only mildly reduced. The ventilatory equivalents decreased early in exercise but remained higher than normal at the *AT* (Fig. 10.37.1, panel 4), consistent with V/Q mismatching. The abnormalities are typical of pulmonary vascular disease limiting cardiac output and impairing normal V/Q matching in the lung. Findings at age 58 (Tables 10.37.2 and 10.37.4 and Fig. 10.37.2) were qualitatively similar, but the abnormalities were more severe, with lower values for peak $\dot{V}O_2$ and *AT*, higher ventilatory equivalents, and lower oxygen saturation readings. Results of serial exercise tests spanning a period of 17 years are summarized in Table 10.37.5. During the first decade of treatment of his pulmonary hypertension, there was progressive increases in peak $\dot{V}O_2$, *AT*, and O_2 pulse, and a decrease in the $\dot{V}E/\dot{V}CO_2$ value measured at the *AT*. Over subsequent years, there was a trend for reduction in peak $\dot{V}O_2$, O_2 pulse, and *AT*, indicative of deteriorating cardiovascular function, and increase in $\dot{V}E/\dot{V}CO_2$ at the *AT*, consistent with worsening V/Q matching.

Conclusion

This case is presented both as an example of typical exercise findings related to pulmonary vascular disease and as a unique longitudinal series over an extended period of observation. The first test shown reflects the patient near his best function; the decline in exercise capacity over the next 8 years is associated with worsening indices of pulmonary gas exchange, reflecting the functional effects of persistent pulmonary vascular disease.

Table 10.37.2

Selected Exercise Data

	Age 50		Age 58	
Measurement	**Predicted**	**Measured**	**Predicted**	**Measured**
Peak $\dot{V}O_2$ (L/min)	2.69	1.66	2.46	1.35
Maximum heart rate (beats/min)	170	133	162	150
Maximum O_2 pulse (mL/beat)	15.8	12.7	15.2	9.9
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.9	10.3	7.8
AT (L/min)	>1.21	0.89	>1.13	0.66
Blood pressure (mm Hg [rest, max])		110/64, 165/84		103/76, 192/118
Maximum $\dot{V}E$ (L/min)		81		78
Exercise breathing reserve (L/min)	>15	42	>15	25
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.7	40.7	27.5	45.7

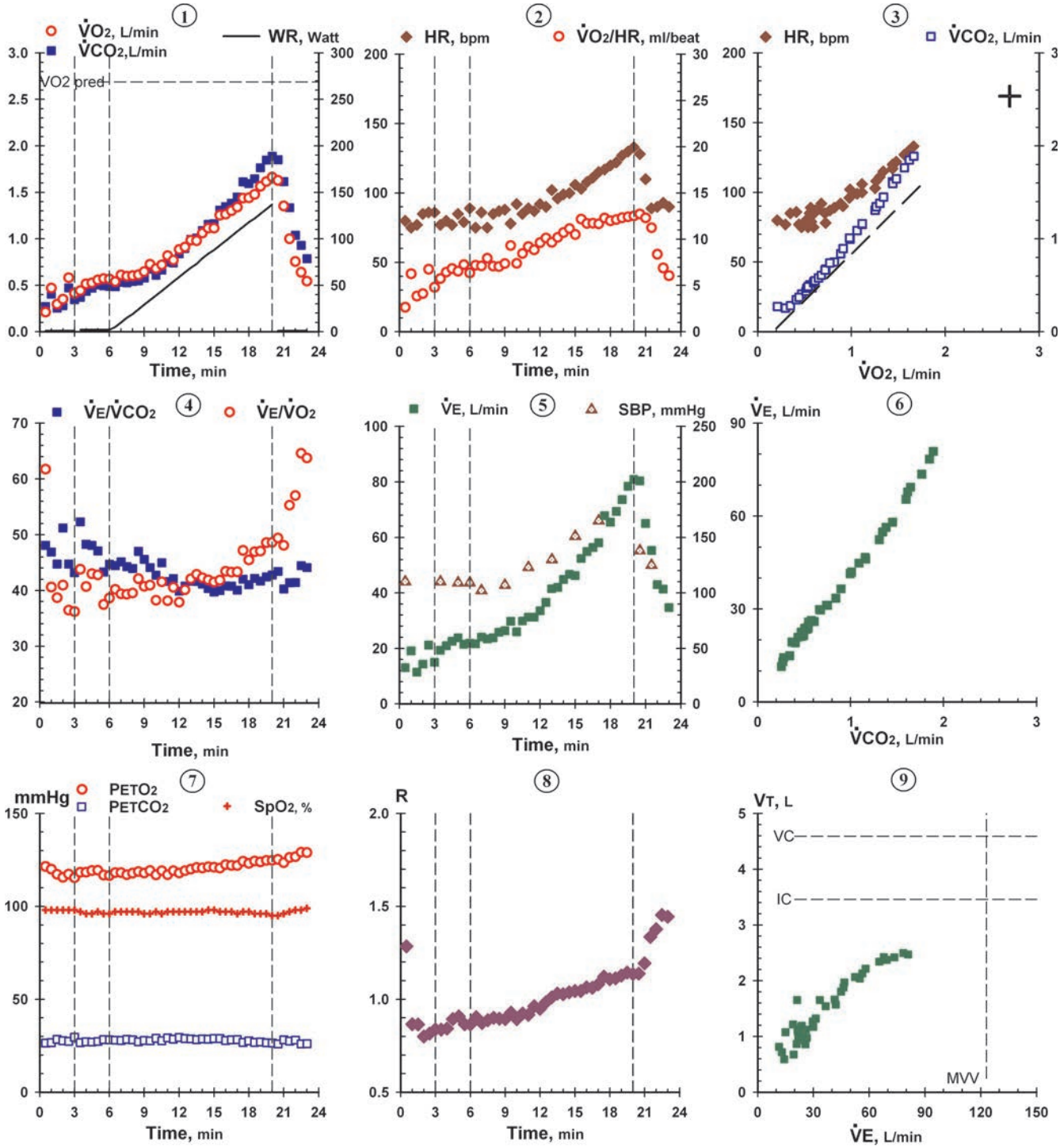

FIGURE 10.37.1. Test performed at age 50. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.37.3

Air Breathing, Age 50

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0																				
0.5	Rest	110/64	80	18	13.0	0.27	0.21	2.6	1.28			121			26			48	62	
1.0	Rest		75	16	19.0	0.41	0.47	6.3	0.87			120			27			47	41	
1.5	Rest		77	14	11.5	0.26	0.30	3.8	0.86			117			28			45	39	
2.0	Rest		85	24	14.3	0.28	0.35	4.1	0.80			116			28			51	41	
2.5	Rest		86	13	21.2	0.47	0.58	6.7	0.82			117			27			45	36	
3.0	Rest		86	14	15.0	0.35	0.41	4.8	0.84			115			30			43	36	
3.5	Unloaded	110/64	77	29	19.4	0.37	0.44	5.7	0.84			118			27			52	44	
4.0	Unloaded		80	24	21.0	0.43	0.52	6.4	0.84			118			27			48	41	
4.5	Unloaded		77	24	22.6	0.47	0.53	6.8	0.89			119			27			48	43	
5.0	Unloaded	109/65	85	24	23.8	0.51	0.56	6.5	0.91			119			27			47	43	
5.5	Unloaded		79	19	21.4	0.50	0.57	7.2	0.87			117			28			43	37	
6.0	Unloaded		89	22	21.9	0.49	0.57	6.4	0.86			117			28			45	39	
6.5	5		75	20	21.6	0.49	0.54	7.2	0.90			118			28			44	40	
7.0	10	102/66	86	23	24.1	0.53	0.61	7.1	0.87			118			28			45	39	
7.5	15		75	20	23.4	0.53	0.60	7.9	0.89			117			28			44	39	
8.0	19		85	20	23.8	0.54	0.60	7.1	0.90			118			28			44	40	
8.5	24		87	30	25.8	0.55	0.61	7.0	0.90			119			27			47	42	
9.0	29	107/69	88	27	26.4	0.58	0.65	7.4	0.89			118			28			46	41	
9.5	34		78	23	29.7	0.67	0.73	9.3	0.93			119			28			44	41	
10.0	39		92	23	25.9	0.61	0.68	7.4	0.89			117			29			43	38	
10.5	44		85	25	29.9	0.66	0.72	8.5	0.92			119			28			45	42	
11.0	49	123/68	89	24	31.2	0.75	0.82	9.2	0.92			117			29			42	38	
11.5	54		87	24	31.2	0.74	0.77	8.9	0.96			119			29			42	41	
12.0	59		92	20	33.5	0.84	0.89	9.6	0.95			118			29			40	38	
12.5	64		90	24	36.5	0.90	0.91	10.1	0.98			119			29			41	40	
13.0	69	130/78	102	25	41.4	1.00	0.99	9.7	1.01			120			29			42	42	
13.5	73		96	27	42.0	1.01	0.98	10.2	1.03			121			28			42	43	
14.0	79		99	25	44.8	1.09	1.06	10.7	1.03			121			29			41	42	
14.5	84		100	24	46.7	1.16	1.11	11.1	1.04			121			28			40	42	
15.0	88	151/80	106	25	46.2	1.16	1.11	10.5	1.04			121			29			40	41	
15.5	93		103	25	52.4	1.31	1.25	12.2	1.04			121			29			40	42	
16.0	98		108	27	54.9	1.35	1.26	11.7	1.06			122			28			41	43	
16.5	103		111	26	56.3	1.38	1.30	11.7	1.06			122			28			41	43	
17.0	108	165/84	115	26	58.1	1.45	1.34	11.7	1.08			122			28			40	43	
17.5	113		117	28	67.8	1.61	1.44	12.3	1.12			124			27			42	47	
18.0	118		120	28	65.5	1.60	1.44	12.0	1.11			123			28			41	45	
18.5	122		122	29	69.4	1.65	1.48	12.1	1.11			124			27			42	47	
19.0	127		127	30	73.6	1.76	1.56	12.3	1.13			124			27			42	47	
19.5	132		130	31	78.4	1.85	1.62	12.4	1.14			125			27			42	49	
20.0	137		133	33	80.9	1.89	1.66	12.5	1.14			125			26			43	49	
20.5	Recovery	138/72	128	32	80.4	1.85	1.63	12.7	1.14			125			26			43	49	
21.0	Recovery		110	25	65.0	1.62	1.35	12.3	1.19			124			28			40	48	
21.5	Recovery	125/68	89	23	55.3	1.34	1.00	11.2	1.34			126			28			41	55	
22.0	Recovery		90	18	43.0	1.04	0.75	8.4	1.38			127			28			41	57	
22.5	Recovery		93	21	41.3	0.93	0.64	6.9	1.45			129			26			44	65	
23.0	Recovery		90	19	34.7	0.79	0.54	6.0	1.44			129			26			44	64	

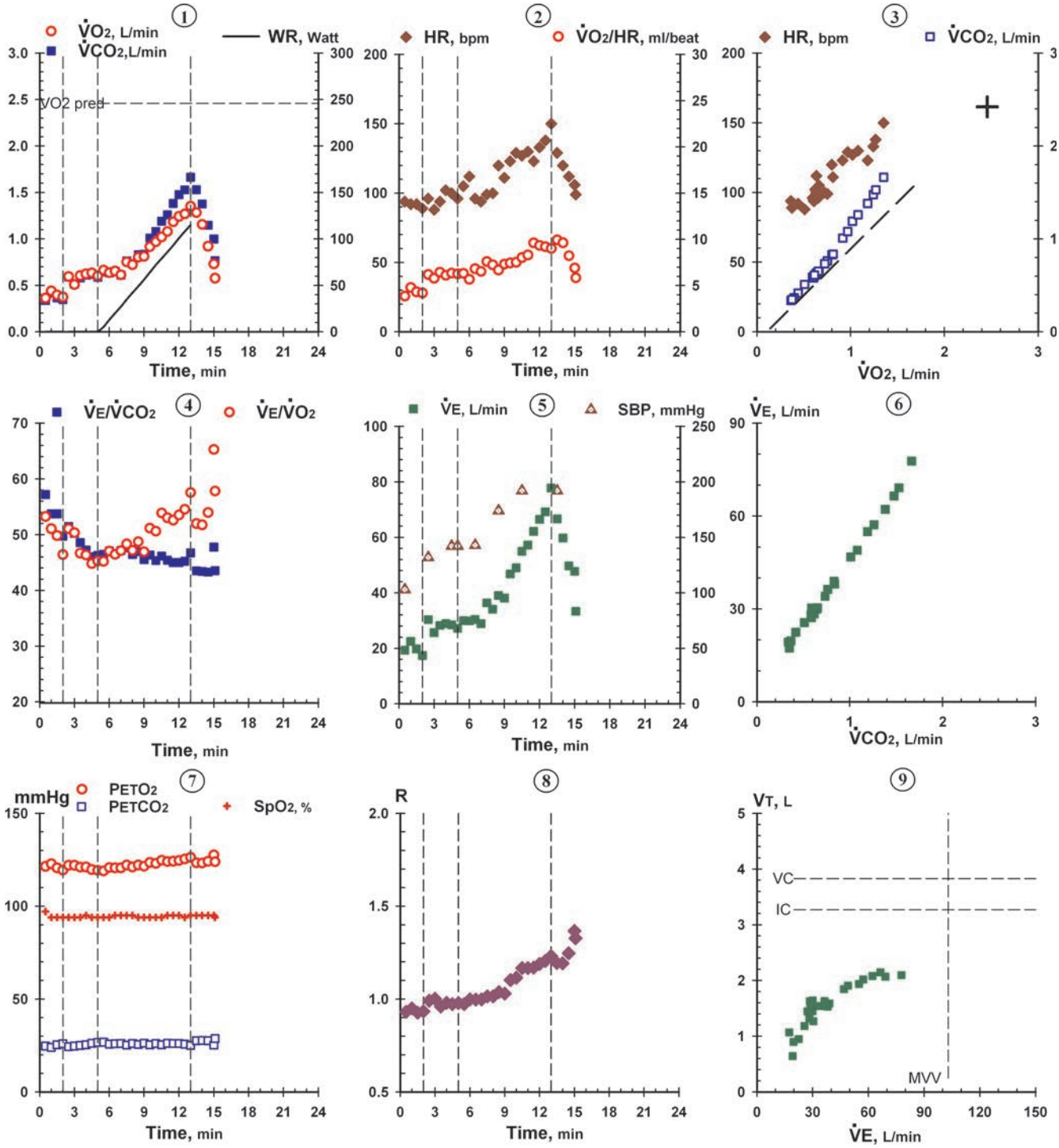

FIGURE 10.37.2. Test performed at age 58. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.37.4

Air Breathing, Age 58

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
0.5	Rest	103/76	94	30	19.3	0.34	0.36	3.9	0.93			121			25			57	53	
1.0	Rest		92	24	22.5	0.42	0.44	4.8	0.95			123			24			54	51	
1.5	Rest		92	22	19.7	0.37	0.40	4.3	0.93			121			25			54	50	
2.0	Rest		89	16	17.4	0.35	0.37	4.2	0.93			119			26			50	46	
2.5	Unloaded	132/98	96	24	30.3	0.59	0.59	6.2	0.99			122			24			51	51	
3.0	Unloaded		88	22	25.6	0.51	0.51	5.8	1.00			122			25			50	50	
3.5	Unloaded		94	21	28.2	0.58	0.61	6.4	0.96			121			25			49	47	
4.0	Unloaded		102	19	28.9	0.61	0.62	6.1	0.98			121			25			47	46	
4.5	Unloaded	142/118	100	18	28.4	0.62	0.63	6.3	0.97			120			26			46	45	
5.0	Unloaded		96	19	27.2	0.59	0.60	6.3	0.98			119			27			46	45	
5.5	5	142/118	105	18	30.0	0.65	0.66	6.3	0.97			119			27			46	45	
6.0	13		112	21	29.9	0.63	0.64	5.7	1.00			121			26			47	47	
6.5	20	143/108	96	20	30.4	0.65	0.65	6.8	1.00			121			26			47	46	
7.0	27		94	20	28.9	0.61	0.61	6.5	1.00			121			26			47	47	
7.5	35		99	22	36.3	0.76	0.75	7.6	1.01			122			25			48	48	
8.0	42		100	22	34.1	0.73	0.72	7.2	1.02			121			26			46	47	
8.5	49	174/96	120	25	39.0	0.83	0.80	6.7	1.04			122			26			47	49	
9.0	56		111	25	38.1	0.84	0.81	7.3	1.03			122			26			46	47	
9.5	64		123	25	46.8	1.01	0.92	7.4	1.10			124			25			46	51	
10.0	72		129	26	49.0	1.08	0.97	7.5	1.12			123			26			45	51	
10.5	79	192/108	127	28	55.0	1.19	1.02	8.0	1.17			125			25			46	54	
11.0	86		130	28	57.2	1.26	1.08	8.3	1.17			124			26			45	53	
11.5	93		123	30	62.2	1.38	1.18	9.6	1.17			124			26			45	53	
12.0	101		133	31	66.5	1.48	1.24	9.3	1.19			125			26			45	54	
12.5	108		138	33	69.2	1.53	1.27	9.2	1.21			125			26			45	55	
13.0	115		150	37	77.8	1.67	1.35	9.0	1.23			126			25			47	58	
13.5	Recovery	192/108	129	29	66.6	1.53	1.28	9.9	1.19			123			28			44	52	
14.0	Recovery		120	27	59.8	1.38	1.16	9.6	1.19			123			28			43	52	
14.5	Recovery		112	23	49.7	1.15	0.92	8.2	1.25			124			28			43	54	
15.0	Recovery		106	28	47.7	1.00	0.73	6.9	1.37			128			25			48	65	
15.5	Recovery		99	16	33.4	0.77	0.58	5.8	1.33			124			29			44	58	

Table 10.37.5

Selected Exercise Data over 17 Years of Treatment for Pulmonary Hypertension

Age (years)	Peak $\dot{V}O_2$ (L/min)	*AT* (L/min)	Peak $\dot{V}O_2$/HR (mL/beat)	$\dot{V}E/\dot{V}CO_2$ at *AT*
41	1.10	0.80	8.5	50
47	1.46	0.95	11.4	42
48	1.55	0.90	12.2	40
49	1.60	0.75	11.3	40
50	1.66	0.89	12.7	41
51	1.68	1.0	13.0	42
52	1.75	0.90	11.5	40
53	1.74	1.10	10.8	43
54	1.64	0.84	10.6	46
55	1.46	0.96	9.6	44
56	1.43	0.95	9.4	41
57	1.45	0.95	9.6	45
58	1.35	0.66	9.9	46

Case 38 Idiopathic Pulmonary Hypertension

CLINICAL FINDINGS

This 47-year-old woman had pulmonary hypertension associated with prior anorexigen use. Exercise testing was performed periodically to assess her functional capacity, which improved gradually over a period of several years of pharmacologic treatment. She was first treated with a calcium channel blocking agent and subsequently transitioned to other therapies. At the time that this test was conducted, she had been treated for pulmonary hypertension for 10 years and reported feeling "great." She performed all her normal daily activities without difficulty and walked for 20 to 30 minutes each day for exercise. Her medications included a prostacyclin analog and a phosphodiesterase inhibitor along with diuretics, warfarin, and a statin. On examination, she was flushed, had a prominent second heart sound, and had trace peripheral edema of the ankles. An ECG showed right ventricular hypertrophy with strain.

EXERCISE FINDINGS

Exercise was performed on a cycle ergometer. After 3 minutes of pedaling at 60 rpm without added load, work rate was continuously increased by 10 W per minute until the patient stopped with symptoms of airway irritation and cough. There were no significant changes to the ECG.

INTERPRETATION

Comments

Pulmonary function tests showed a mild ventilatory defect and a low-normal DLCO (Table 10.38.1).

Analysis

Peak $\dot{V}O_2$ and anaerobic threshold were both reduced (Tables 10.38.2 and 10.38.3). In addition, the rate of increase of $\dot{V}O_2$ relative to work rate was less than normal and the rate of increase of heart rate relative to $\dot{V}O_2$ was steeper than normal (Fig. 10.38.1, panels 1 and 3). The O_2 pulse increased very little during exercise and the peak value was low. These findings are all consistent with an impairment of O_2 flow. Because the patient reported that she stopped exercise due to airway irritation, rather than due to systemic symptoms, the peak values might underestimate her true maximal exercise capacity. Even if so, the anaerobic threshold and the rate of change of $\dot{V}O_2$ relative to work rate and heart rate relative to $\dot{V}O_2$ indicate abnormal O_2 flow in response to the exercise stress. Similarly, ventilation was high relative to metabolic rate throughout exercise, as reflected in the $\dot{V}E/\dot{V}CO_2$ at the *AT* of 42, indicative of areas of high V:Q in the lung. The findings of abnormal oxygen flow and elevated ventilatory requirements are characteristic of pulmonary vascular disease. The typical findings of exercise-induced

Table 10.38.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		47
Sex		Female
Height (cm)		160
Weight (kg)		74
VC (L)	3.12	2.68
IC (L)	2.08	2.40
FEV_1 (L)	2.6	1.87
FEV_1/VC (%)	83	70
MVV (L/min)	97	85
DLCO (mL/mm Hg/min)	22.7	19.8

Table 10.38.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.61	0.89
Maximum heart rate (beats/min)	173	136
Maximum O_2 pulse (mL/beat)	9.3	7.0
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.3	5.4
AT (L/min)	>0.79	0.72
Blood pressure (mm Hg [rest, max])		107/76, 125/88
Maximum $\dot{V}E$ (L/min)		40
Exercise breathing reserve (L/min)	>15	45
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.2	42.2

right-to-left shunt (illustrated in Case 36 of this chapter) are not evident in this patient. Indeed, although oxygen saturation, estimated by pulse oximeter, was low at rest, it increased during exercise. Although this is not a usual feature of pulmonary vascular disease, it is characteristic of overcoming peripheral atelectasis in centrally obese patients when breathing deeply. The markedly reduced expiratory reserve volume (see Table 10.38.1) is consistent with this process. This does not negate the evidence for pulmonary vasculopathy as the primary cause of exercise intolerance as revealed by panels 4 (high ventilatory equivalents), 6 (steep $\dot{V}E$ vs. $\dot{V}CO_2$), and 7 (reduced $PETCO_2$) during exercise.

Conclusion

This case is presented to illustrate findings typical of pulmonary vascular disease. The abnormal cardiorespiratory responses persist despite symptomatic improvement with pulmonary vasodilator therapy.

Table 10.38.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{VD}{VT}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	107/76	89	16	16.8	0.37	0.42	4.7	0.87			120			24			46	40	
1.0	Rest		87	15	15.4	0.35	0.42	4.8	0.83			118			24			44	37	
1.5	Rest		86	15	13.0	0.29	0.36	4.2	0.81			115			25			45	36	
2.0	Rest		84	18	14.6	0.32	0.38	4.5	0.83			117			24			46	39	
2.5	Rest		86	15	14.3	0.32	0.40	4.6	0.80			116			25			45	36	
3.0	Rest		84	16	13.9	0.31	0.37	4.4	0.83			117			24			45	37	
3.5	Unloaded	107/76	88	22	14.8	0.31	0.39	4.4	0.81			115			25			47	38	
4.0	Unloaded		93	23	18.5	0.38	0.43	4.7	0.88			120			23			49	43	
4.5	Unloaded		94	22	18.2	0.39	0.44	4.7	0.88			120			23			47	41	
5.0	Unloaded		96	21	19.5	0.43	0.52	5.4	0.83			118			24			46	38	
5.5	Unloaded	113/73	98	22	20.1	0.44	0.53	5.4	0.83			118			24			46	38	
6.0	Unloaded		98	22	19.6	0.43	0.53	5.4	0.82			117			24			46	37	
6.5	3		100	22	20.5	0.45	0.55	5.5	0.81			117			25			46	37	
7.0	8		100	22	21.1	0.47	0.57	5.7	0.83			118			25			45	37	
7.5	12		100	21	20.3	0.46	0.56	5.6	0.81			116			25			44	36	
8.0	17		102	22	21.1	0.48	0.57	5.6	0.84			117			25			44	37	
8.5	22	125/79	102	22	21.2	0.48	0.58	5.7	0.83			117			25			44	36	
9.0	27		106	21	21.7	0.50	0.60	5.7	0.83			117			25			43	36	
9.5	32		107	22	22.7	0.53	0.63	5.8	0.84			117			25			43	36	
10.0	37		109	22	23.8	0.56	0.66	6.0	0.85			117			25			43	36	
10.5	42		110	22	24.2	0.58	0.67	6.1	0.86			117			26			42	36	
11.0	47		117	21	25.9	0.62	0.72	6.2	0.86			117			26			42	36	
11.5	52		119	23	28.1	0.68	0.75	6.3	0.90			118			26			42	37	
12.0	57		122	23	29.1	0.72	0.77	6.3	0.93			119			26			41	38	
12.5	62		130	25	33.1	0.81	0.82	6.3	0.98			120			26			41	40	
13.0	67		132	26	36.0	0.87	0.86	6.5	1.01			121			26			42	42	
13.5	70		136	28	39.6	0.95	0.89	6.6	1.06			123			25			42	44	
14.0	Recovery	125/88	119	29	37.9	0.92	0.83	7.0	1.10			123			25			41	45	
14.5	Recovery		112	25	31.8	0.79	0.69	6.1	1.14			123			25			40	46	
15.0	Recovery	121/88	104	28	29.0	0.67	0.54	5.2	1.23			126			24			44	54	
15.4	Recovery		100	24	24.7	0.55	0.46	4.6	1.22			126			24			45	54	

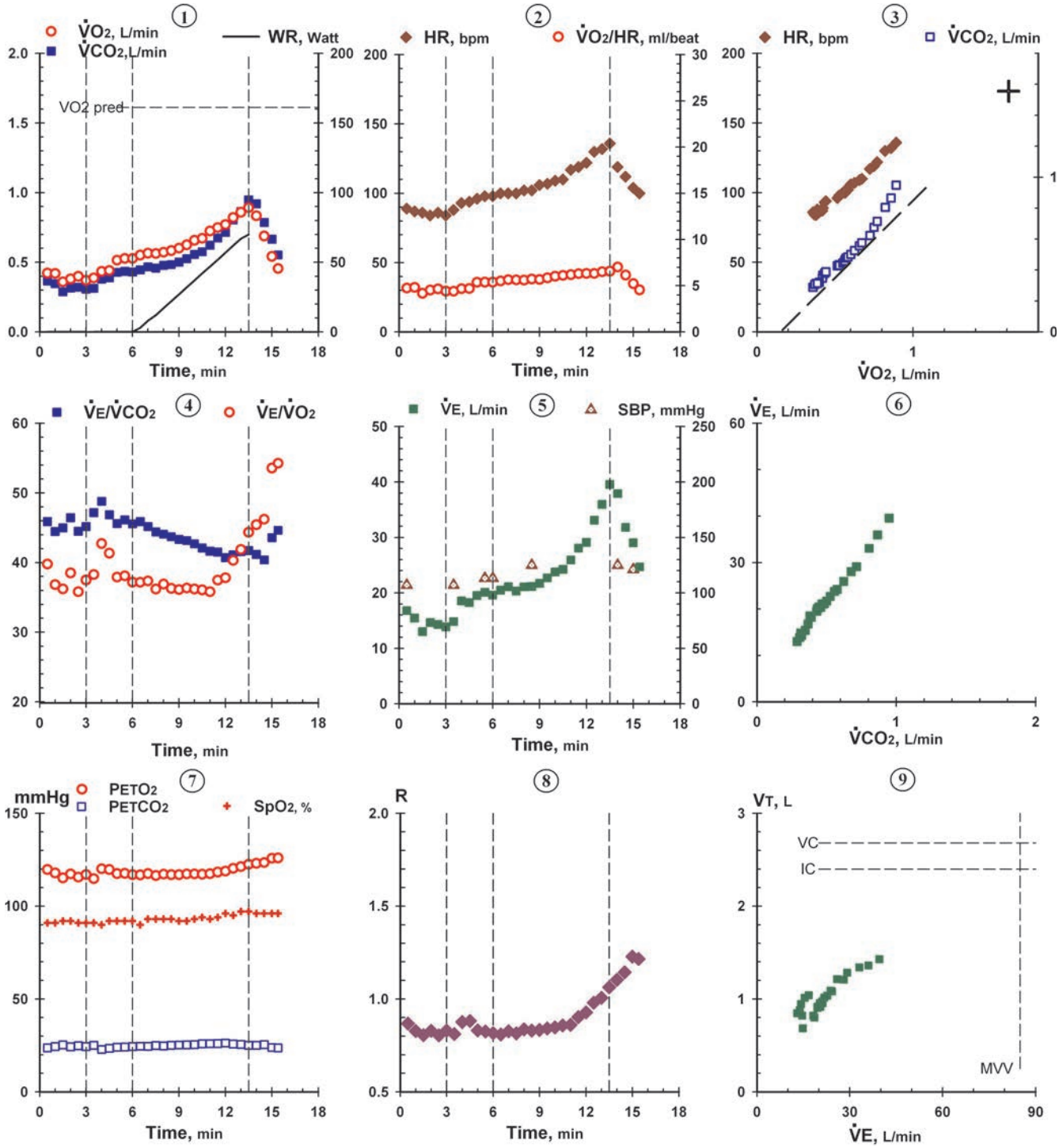

FIGURE 10.38.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 39 Mixed Connective Tissue Disease with Pulmonary Involvement

CLINICAL FINDINGS

This 38-year-old man with known mixed connective tissue disease and restrictive lung function was referred for exercise testing to determine his level of disability. He has had a productive cough for 3 years and had been dyspneic for over 2 years. He has never smoked but had been exposed to multiple chemical agents in a rubber factory. His medications at the time of testing were prednisone, theophylline, and cimetidine.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 15 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously inserted brachial artery catheter. Resting ECG was normal except for occasional premature ectopic beats, which increased in frequency to a maximum of 12 per minute near peak exercise. No ST-segment or T-wave abnormalities occurred. Exercise was stopped because the patient seemed unsteady and indicated that he was lightheaded. These symptoms cleared within a few minutes of ending exercise. He indicated that he was also out of breath but did not identify this as limiting at the time the test ended.

INTERPRETATION

Comments

The resting respiratory function studies show severe restriction with severe loss of effective pulmonary capillary bed (Table 10.39.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), the patient had a low peak $\dot{V}O_2$ and an extremely low anaerobic threshold (Table 10.39.2). In Flowchart 4 (Fig. 8.4), branch point 4.1 distinguishes between low or normal breathing reserve. In this case, it is low using the indirect MVV. Although breathing reserve would be normal if based on the directly measured MVV (as shown in Fig. 10.39.1, panel 9), the direct MVV appears inappropriately high. Classifying the breathing reserve as low would lead through branch point 4.2 to the category of exercise limitation due to lung disease, based on impaired peripheral oxygenation and high VD/VT (Tables 10.39.2 and 10.39.3). Other findings consistent with ventilatory limitation were the very high breathing frequency (64 breaths per minute) and high VT/IC. This is consistent with the patient's clinical diagnosis. If breathing reserves were instead classified as normal at branch point 4.1 of the flowchart, this would lead to the category of abnormal pulmonary circulation at branch point 4.3 by the finding of high ventilatory equivalents. This conclusion would also be reasonable. In addition to the findings related to breathing and pulmonary

Table 10.39.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		38
Sex		Male
Height (cm)		188
Weight (kg)	88	88
Hematocrit (%)		43
VC (L)	5.09	2.28
IC (L)	3.39	1.36
TLC (L)	7.14	3.43
FEV_1 (L)	4.09	1.99
FEV_1/VC (%)	81	87
MVV (L/min)		
Direct	163	107
Indirect	164	80
DLCO (mL/mm Hg/min)	32.7	10.7

Table 10.39.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	3.21	1.07
Maximum heart rate (beats/min)	182	128
Maximum O_2 pulse (mL/beat)	17.6	8.4
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	>10.3	7.3
AT (L/min)	>1.35	0.60
Blood pressure (mm Hg [rest, max ex])		141/90, 222/102
Maximum $\dot{V}E$ (L/min)		76
Exercise breathing reserve (L/min)		
Using direct MVV	>15	31
Using indirect MVV	>15	4
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	25.2	38.5
PaO_2 (mm Hg [rest, max ex])		79, 63
$P(A-a)O_2$ (mm Hg [rest, max ex])		16, 58
$PaCO_2$ (mm Hg [rest, max ex])		40, 39
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		5, 9
VD/VT (rest, max ex)		0.46, 0.48
HCO_3^- (mEq/L [rest, recov])		25, 20

gas exchange abnormalities, the test was remarkable for severe reduction in peak $\dot{V}O_2$ and O_2 pulse as compared to predicted, and for the failure of $\dot{V}O_2$ to increase appropriately with the increasing work rate (see Fig. 10.39.1, panels 1, and 2). These findings are characteristic of impaired oxygen flow due to cardiovascular disease. This is further manifest in the slow recovery of $\dot{V}O_2$ and O_2 pulse toward baseline during recovery, reflecting the need to reverse the consequences of the accumulated oxygen deficit in the tissues. Consistent with this, R decreased rather than increased in early recovery (see Fig. 10.39.1, panel 8) due to $\dot{V}O_2$ decreasing more slowly than $\dot{V}CO_2$. The progressive arterial hypoxemia and high VD/VT support the conclusion that the patient's primary limitation is pulmonary arterial occlusive disease. The occurrences of ectopy and lightheadedness suggest impaired perfusion and/or oxygenation of the heart and brain during high-intensity exercise.

Conclusion

Significant defects were demonstrated in breathing mechanics, pulmonary gas exchange, and cardiovascular responses, attributable to interstitial lung disease with secondary effects on the pulmonary vasculature. The increased CO_2 production resulting from bicarbonate buffering of early onset of lactic acidosis (due to cardiovascular impairment), together with high VD/VT, resulted in an exceptionally high ventilatory requirement. The increased VD/VT and arterial hypoxemia, accompanied by the reduced ventilatory capacity due to lung restriction, was the likely cause of his breathlessness with exercise.

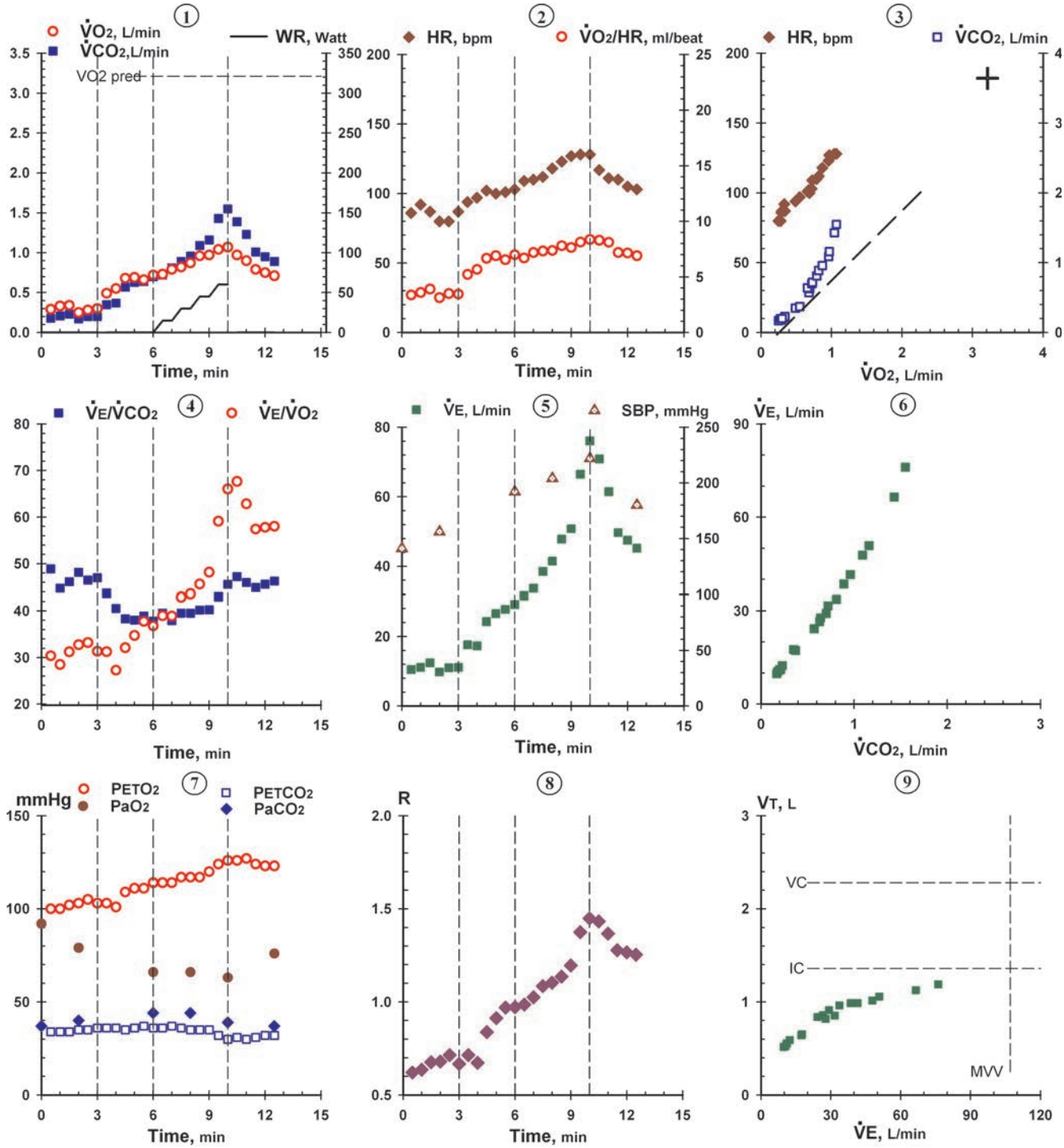

FIGURE 10.39.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.39.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	141/90								7.45	25		92			37				
0.5	Rest		86	20	10.5	0.18	0.29	3.4	0.62			100			34			49	30	
1.0	Rest		92	20	11.1	0.21	0.33	3.6	0.64			100			34			45	28	
1.5	Rest		87	21	12.4	0.23	0.34	3.9	0.68			102			34			46	31	
2.0	Rest	156/96	80	19	9.8	0.17	0.25	3.1	0.68	7.41	25	103	79	16	35	40	5	48	33	0.46
2.5	Rest		80	20	11.0	0.20	0.28	3.5	0.71			105			35			47	33	
3.0	Rest		87	20	11.1	0.20	0.30	3.4	0.67			103			36			47	31	
3.5	Unloaded		94	27	17.6	0.35	0.49	5.2	0.71			103			36			44	31	
4.0	Unloaded		97	27	17.3	0.37	0.55	5.7	0.67			101			36			41	27	
4.5	Unloaded		102	29	24.3	0.57	0.68	6.7	0.84			109			35			38	32	
5.0	Unloaded		100	31	26.6	0.63	0.69	6.9	0.91			111			36			38	35	
5.5	Unloaded		101	34	27.8	0.64	0.66	6.5	0.97			111			37			39	38	
6.0	Unloaded	192/99	103	32	29.2	0.70	0.72	7.0	0.97	7.38	26	114	66	39	36	44	8	38	37	0.44
6.5	15		109	37	31.6	0.72	0.73	6.7	0.99			114			36			40	39	
7.0	15		110	35	33.7	0.81	0.79	7.2	1.03			114			37			38	39	
7.5	30		112	39	38.5	0.89	0.82	7.3	1.09			117			36			40	43	
8.0	30	204/102	118	42	41.5	0.96	0.87	7.4	1.10	7.38	26	117	66	43	35	44	9	40	44	0.46
8.5	45		123	47	47.8	1.09	0.96	7.8	1.14			117			35			40	46	
9.0	45		127	48	50.8	1.16	0.97	7.6	1.20			120			35			40	48	
9.5	60		128	59	66.5	1.43	1.04	8.1	1.38			124			32			43	59	
10.0	60	222/102	128	64	76.1	1.55	1.07	8.4	1.45	7.38	23	126	63	58	30	39	9	46	66	0.48
10.5	Recovery		117	62	70.9	1.39	0.97	8.3	1.43			126			31			47	68	
11.0	Recovery		111	58	61.5	1.23	0.90	8.1	1.37			127			30			46	63	
11.5	Recovery		110	51	49.7	1.01	0.79	7.2	1.28			124			31			45	57	
12.0	Recovery		105	49	47.5	0.95	0.75	7.1	1.27			123			32			46	58	
12.5	Recovery	180/88	103	47	45.2	0.89	0.71	6.9	1.25	7.35	20	123	76	43	32	37	5	46	58	0.45

Case 40 Pulmonary and Systemic Vasculitis: Air and Oxygen Breathing Studies

CLINICAL FINDINGS

This 54-year-old executive had apparently been in good health until 11 years previously, when he had an acute myocardial infarction. A coronary arteriogram was normal 1 year later. Five years later, he developed widespread signs and symptoms of vasculitis with fatigue, jaundice, Raynaud phenomenon, peripheral neuropathy, and renal failure due to membranoproliferative glomerulonephritis. Diffuse cerebritis with panhypopituitarism had followed. His disease had responded well to corticosteroids, cyclophosphamide, and endocrine replacement therapy. Progressive exertional dyspnea began 3 years prior to this evaluation. A biopsy of a pulmonary nodule showed organizing exudate, hemorrhage, and severe arteriolar wall thickening. The patient never smoked or abused drugs or alcohol. Physical examination revealed acrocyanosis without clubbing, clear lungs, and normal heart sounds. Exercise testing was performed to evaluate the possible efficacy of supplemental oxygen.

EXERCISE FINDINGS

The patient performed two exercise tests on the cycle ergometer. On both occasions, he first pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 15 W every minute. The first test was done during air breathing and the second while breathing 100% oxygen. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously inserted brachial artery catheter.

During air breathing, the patient stopped exercise because of leg fatigue and complained of shortness of breath. While breathing 100% O_2 the patient ended the test with the complaint of leg fatigue only. Resting ECG showed a rightward axis, poor R-wave progression in the precordial leads, and T-wave inversion in V_4. There was no ectopy or abnormality of ST segments, although the T-wave inversions deepened during exercise.

INTERPRETATION

Comments

Except for the very low diffusing capacity, the results of this patient's respiratory function studies were normal (Table 10.40.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), during air breathing, the peak $\dot{V}O_2$ and anaerobic threshold were significantly reduced (Table 10.40.2). Referring to Flowchart 4 (Fig. 8.4), the breathing reserve was normal (branch point 4.1). The $\dot{V}E/\dot{V}CO_2$ at the *AT* was significantly increased (Fig. 10.40.1, Table 10.40.3) (branch point 4.3), leading to the category of abnormal pulmonary circulation. The next branch point (4.5) is based on arterial oxygenation. Although SaO_2 was not significantly reduced, $P(A-a)O_2$ was higher than normal (Table 10.40.3). If oxygenation were categorized as normal, this points to left ventricular heart failure and, if reduced, to pulmonary vascular disease. The latter is most consistent with the clinical history and low DLCO. Other measurements consistent with pulmonary vascular disease include the high VD/VT, which increased with exercise rather than decreasing as is normal, increased $P(a-ET)CO_2$, and $P(A-a)O_2$ at the maximum work rate. The steep heart rate–$\dot{V}O_2$ relationship, low O_2 pulse, and decreasing $\Delta\dot{V}O_2/\Delta WR$ as work rate progressed are findings consistent with a number of cardiovascular conditions, including pulmonary vascular disease.

The arterial blood gases at rest showed a compensated metabolic acidosis, likely due to the patient's renal impairment. The metabolic acidosis worsened with the

Table 10.40.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		54
Sex		Male
Height (cm)		170
Weight (kg)	74	64
Hematocrit (%)		38
VC (L)	4.03	4.07
IC (L)	2.68	3.16
FEV_1 (L)	3.18	3.38
FEV_1/VC (%)	79	83
MVV (L/min)	137	143
DLCO (mL/mm Hg/min)	26.5	8.0

Table 10.40.2

Selected Exercise Data

Measurement	Predicted	Room air	Oxygen
Maximum work rate (W)	160	90	90
Peak $\dot{V}O_2$ (L/min)	2.11	0.96	
Maximum heart rate (beats/min)	166	132	131
Maximum O_2 pulse (mL/beat)	12.7	7.3	
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.8	
AT (L/min)	>0.91	<0.75	
Blood pressure (mm Hg [rest, max])		129/69, 204/84	126/75, 201/87
Maximum $\dot{V}E$ (L/min)		117	89
Exercise breathing reserve (L/min)	>15	26	54
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.5	53.4	53.2
PaO_2 (mm Hg [rest, max ex])		114, 90	692, 678
$P(A-a)O_2$ (mm Hg [rest, max ex])		10, 41	−8, 4
$PaCO_2$ (mm Hg [rest, max ex])		26, 25	29, 31
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		7, 9	10, 12
VD/VT (rest, heavy ex)		0.44, 0.52	0.52, 0.57
HCO_3^- (mEq/L [rest, 2-min recov])		18, 12	18, 15

addition of exercise-induced lactic acidosis (see Table 10.40.2). Of note, although PaO_2 decreased during exercise, it remained within the normal range (Table 10.40.3), but the exercise $P(A-a)O_2$ values were mildly abnormal. The PaO_2 values measured during exercise with the patient breathing 100% O_2 (Table 10.40.4 and Fig. 10.40.2) confirmed the absence of the development of a right-to-left shunt (branch point 4.7). The $PaCO_2$ values were systematically higher on the O_2 breathing study, and ventilation at peak exercise was lower, reflecting a decrease in ventilatory drive with favorable effects on the patient's dyspnea. Breathing 100% O_2 had little effect on peak exercise performance, however. Failure to improve peak exercise performance with O_2 breathing despite the reduction in peak ventilatory response suggests that the patient was not primarily ventilatory limited on the air breathing test but was instead limited by cardiovascular factors.

Conclusion

Severe pulmonary vascular disease limited this patient's exercise performance by constraint on cardiac output, as evidenced by the $\dot{V}O_2$-related variables. Analysis of ventilation and arterial blood gases demonstrate that the major gas exchange abnormality was elevated VD/VT with augmented ventilatory requirements but relatively little impairment in oxygenation.

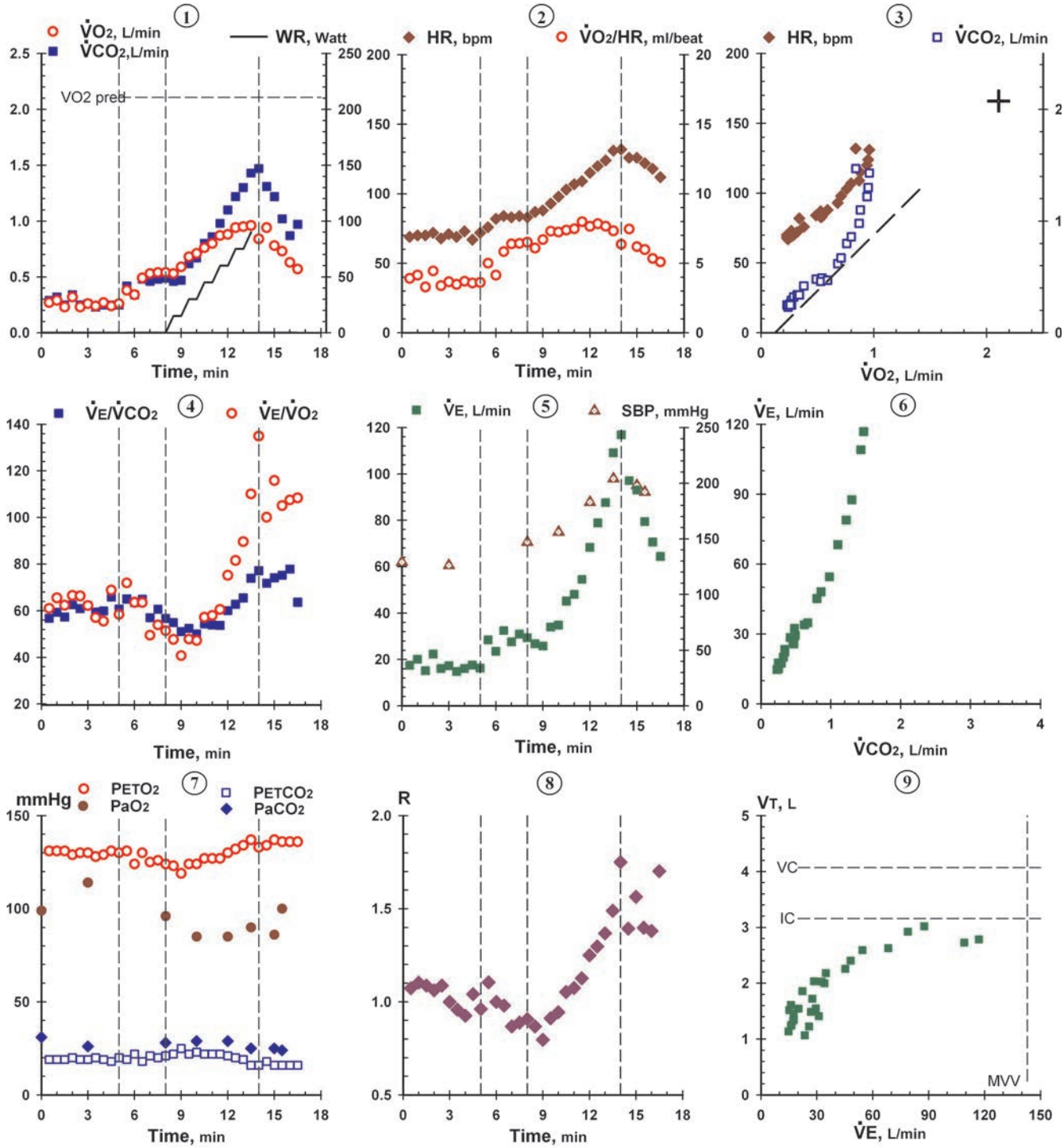

FIGURE 10.40.1. Air breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.40.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	129/69								7.38	18		99			31				
0.5	Rest		69	12	17.5	0.29	0.27	3.9	1.07			131			19			57	61	
1.0	Rest		70	13	20.1	0.32	0.29	4.1	1.10			131			19			59	66	
1.5	Rest		70	10	15.2	0.25	0.23	3.3	1.09			131			19			57	62	
2.0	Rest		72	12	22.3	0.34	0.32	4.4	1.06			129			20			63	67	
2.5	Rest		68	10	16.1	0.25	0.23	3.4	1.09			130			19			61	66	
3.0	Rest	126/69	71	13	17.3	0.26	0.26	3.7	1.00	7.44	17	130	114	10	19	26	7	62	62	0.44
3.5	Rest		69	13	14.8	0.23	0.24	3.5	0.96			128			20			60	57	
4.0	Rest		73	13	16.1	0.25	0.27	3.7	0.93			129			19			60	56	
4.5	Rest		67	13	17.6	0.25	0.24	3.6	1.04			131			18			66	69	
5.0	Rest		72	13	16.3	0.25	0.26	3.6	0.96			130			20			61	58	
5.5	Unloaded		76	14	28.52	0.42	0.38	5.0	1.11			131			19			65	72	
6.0	Unloaded		82	22	23.5	0.34	0.34	4.1	1.00			124			22			64	64	
6.5	Unloaded		84	16	32.5	0.48	0.49	5.8	0.98			130			18			65	64	
7.0	Unloaded		83	16	27.6	0.46	0.53	6.4	0.87			125			21			57	50	
7.5	Unloaded		84	22	31.0	0.48	0.54	6.4	0.89			126			20			61	54	
8.0	Unloaded	147/75	83	19	29.4	0.49	0.54	6.5	0.91	7.41	17	124	96	24	21	28	7	57	51	0.43
8.5	15		87	18	26.8	0.46	0.53	6.1	0.87			123			22			55	48	
9.0	15		88	21	25.8	0.47	0.59	6.7	0.80			119			25			51	41	
9.5	30		93	17	34.0	0.62	0.68	7.3	0.91			124			22			53	48	
10.0	30	156/78	98	16	34.9	0.67	0.71	7.2	0.94	7.39	17	124	85	35	23	29	6	50	47	0.39
10.5	45		103	20	45.2	0.80	0.76	7.4	1.05			127			22			54	57	
11.0	45		107	20	48.1	0.86	0.80	7.5	1.08			127			22			54	58	
11.5	60		109	21	54.5	0.98	0.87	8.0	1.13			127			22			54	64	
12.0	60	183/84	115	26	68.3	1.10	0.88	7.7	1.25	7.38	17	130	85	41	21	29	8	60	75	0.49
12.5	75		120	27	78.9	1.22	0.94	7.8	1.30			132			20			63	81	
13.0	75		124	29	87.6	1.30	0.95	7.7	1.37			134			19			65	90	
13.5	90	204/84	131	40	109.1	1.43	0.96	7.3	1.49	7.38	15	137	90	41	16	25	9	74	110	0.52
14.0	Recovery		132	42	116.9	1.47	0.84	6.4	1.75			133			16			77	135	
14.5	Recovery		126	36	97.1	1.31	0.94	7.5	1.39			134			18			72	100	
15.0	Recovery	198/87	126	32	93.1	1.22	0.78	6.2	1.56	7.37	14	137	86	46	16	25	9	74	116	0.52
15.5	Recovery	192/78	122	32	79.4	1.02	0.73	6.0	1.40	7.33	12	136	100	31	16	24	8	75	105	0.50
16.0	Recovery		118	34	70.6	0.87	0.63	5.3	1.38			136			16			78	107	
16.5	Recovery		112	31	64.4	0.97	0.57	5.1	1.70			136			16			64	108	

Table 10.40.4

Oxygen Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest		88	11	21.0	0.29									20			69		
0.5	Rest		83	12	16.1	0.23									20			66		
1.0	Rest		84	11	16.9	0.25									19			64		
1.5	Rest		86	12	16.2	0.23									19			66		
2.0	Rest		86	16	16.4	0.23									20			65		
2.5	Rest	120/72	84	12	16.9	0.24				7.40	18		692	–8	19	29	10	66		0.52
3.0	Rest		81	12	17.5	0.25									18			66		
3.5	Rest		86	12	23.5	0.31									17			73		
4.0	Unloaded		99	27	14.6	0.16									20			77		
4.5	Unloaded		91	22	30.2	0.40									19			71		
5.0	Unloaded		91	18	16.0	0.23									22			63		
5.5	Unloaded		90	25	21.4	0.35									23			55		
6.0	Unloaded		93	19	24.9	0.41									23			57		
6.5	Unloaded	132/72	91	19	22.3	0.39				7.36	19		678	1	24	34	10	53		0.48
7.0	15		94	16	25.4	0.45									24			53		
7.5	15		96	16	30.4	0.55									23			53		
8.0	30		99	17	32.7	0.59									23			53		
8.5	30	156/75	100	19	38.4	0.65				7.35	18		645	34	24	34	10	57		0.53
9.0	45		105	27	72.3	1.13									25			62		
9.5	45		107	21	43.3	0.73									22			57		
10.0	60		113	24	51.4	0.85									21			58		
10.5	60	189/81	117	27	60.1	0.93				7.35	18		683	–3	20	33	13	62		0.56
11.0	75		120	30	58.1	0.93									27			60		
11.5	75		124	32	72.0	1.08									20			64		
12.0	90		127	37	84.3	1.19									20			68		
12.5	90	201/87	131	43	89.4	1.26				7.34	16		678	4	19	31	12	68		0.57
13.0	Recovery		127	29	71.7	1.11									21			62		
13.5	Recovery		123	32	76.5	1.12									20			66		
14.0	Recovery		121	30	70.8	0.99									18			69		
14.5	Recovery	186/78	118	30	62.9	0.78				7.31	15		682	0	19	31	21	77		0.61
15.0	Recovery		111	32	48.3	0.62									19			74		

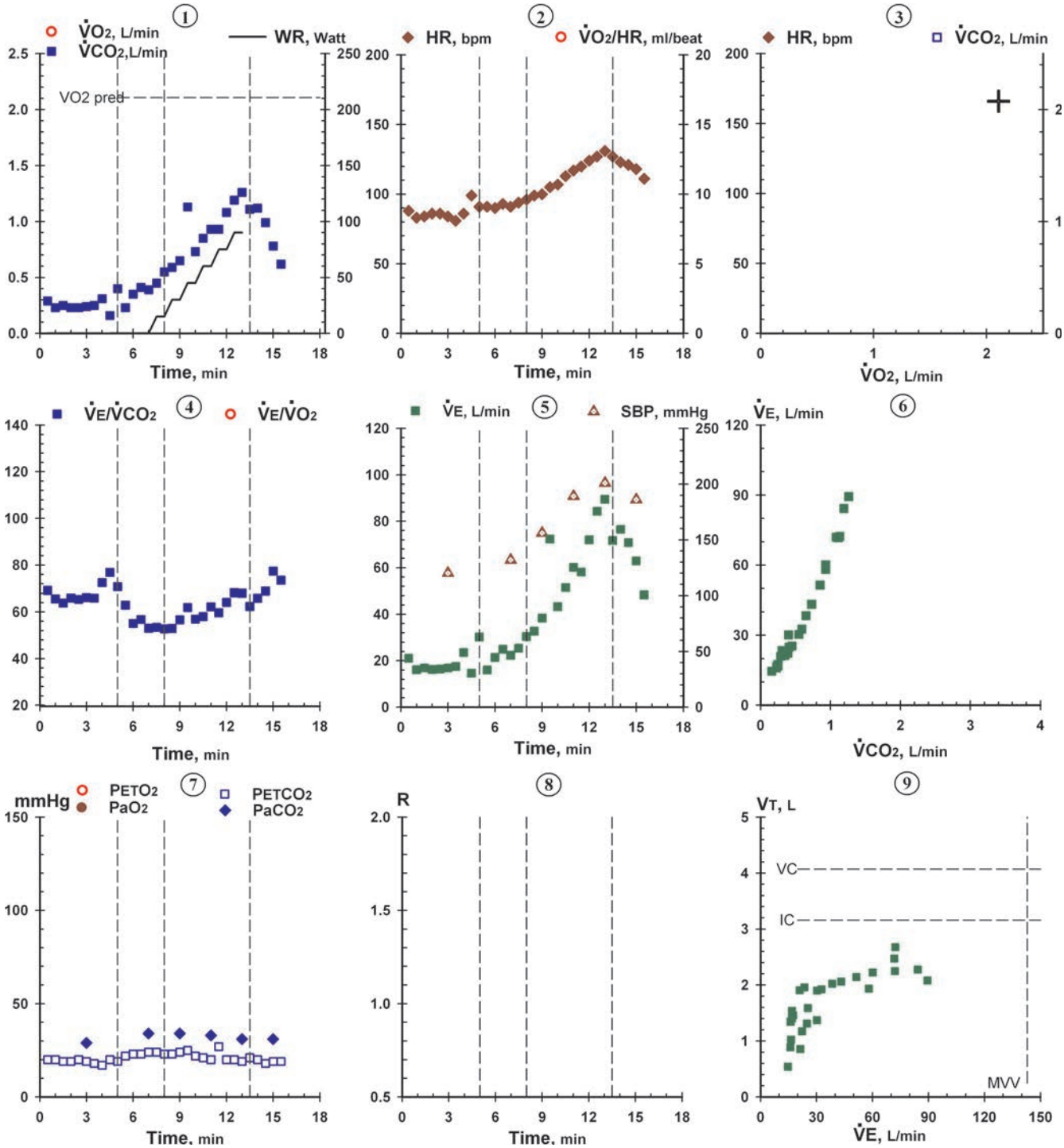

FIGURE 10.40.2. Oxygen breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate the beginning of unloaded cycling, the start of increasing work rate at 15 W per minute, and the start of recovery. Oxygen uptake data are not shown because of technical limitations of calculation with very high-inspired oxygen levels.

Case 41 Scleroderma with Pulmonary and Pulmonary Vascular Involvement

CLINICAL FINDINGS

This 40-year-old woman had a diagnosis of CREST (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia) variant of scleroderma for 2.5 years with symptoms of nonproductive cough, dyspnea on walking one block, Raynaud phenomenon, and difficulty swallowing. She had lost 10 lb over the preceding year due to dysphagia. Chest imaging showed interstitial changes and areas of bronchiectasis. Medications included prednisone, hydroxychloroquine, nifedipine, and sildenafil. The physical exam was notable for fine crackles audible in the lung bases, regular cardiac rhythm, and skin changes characteristic of scleroderma. There was clubbing of the fingers but no peripheral edema. An ECG showed a sinus rhythm and an intraventricular conduction delay.

EXERCISE FINDINGS

The patient exercised on cycle ergometer beginning with 3 minutes of unloaded cycling, followed by continuous increase of the work rate by 10 W per minute. She stopped at a work rate of 47 W due to shortness of breath. An ECG showed occasional ectopic beats during heavy exercise and early recovery but no other changes.

Comments

Pulmonary function testing showed a moderate restrictive defect with a severe reduction in DLCO (Table 10.41.1). An echocardiogram obtained 1 year prior to this test showed normal left and right ventricular systolic function but mild diastolic dysfunction and a normal estimated right ventricular systolic pressure of 22 mm Hg.

Analysis

Peak $\dot{V}O_2$ and *AT* were both low (Table 10.41.2) and there was little increase in $\dot{V}O_2$ as the work rate was incremented (low $\Delta\dot{V}O_2/\Delta WR$; Fig. 10.41.1, panel 1). Heart rate increased steeply relative to $\dot{V}O_2$ and the oxygen pulse reached a stable and nonchanging value at a level lower than the predicted maximum (Fig. 10.41.1, panels 2 and 3). These findings indicate impaired oxygen delivery in response to exercise. The pulse oximeter signal was intermittent due to the patient's sclerodactyly, but SaO_2 was above 90% whenever an acceptable signal was obtained. The low oxygen pulse and $\Delta\dot{V}O_2/\Delta WR$ are thus not likely attributable to low arterial oxygen content and more likely reflect impaired stroke volume and cardiac output. The breathing pattern was rapid and shallow, with respiratory rate climbing into the 50s during the initial phase of unloaded cycling (Table 10.41.3). This

Table 10.41.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		40
Sex		Female
Height (cm)		140
Weight (kg)		43
Hematocrit (%)		41.1
VC (L)	2.57	1.24
IC (L)	1.72	0.92
TLC (L)	3.65	2.33
FEV_1 (L)	2.23	1.08
FEV_1/VC (%)	87	87
MVV (L/min)	88	48
DLCO (mL/mm Hg/min)	19.3	4.4

Table 10.41.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.41	0.62
Maximum heart rate (beats/min)	180	133
Maximum O_2 pulse (mL/beat)	7.8	5.4
	10.3	3.5
AT (L/min)	>0.66	0.47
Blood pressure (mm Hg [rest, max])		129/72, 145/93
Maximum $\dot{V}E$ (L/min)		30
Exercise breathing reserve (L/min)	>15	18
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.2	49.5

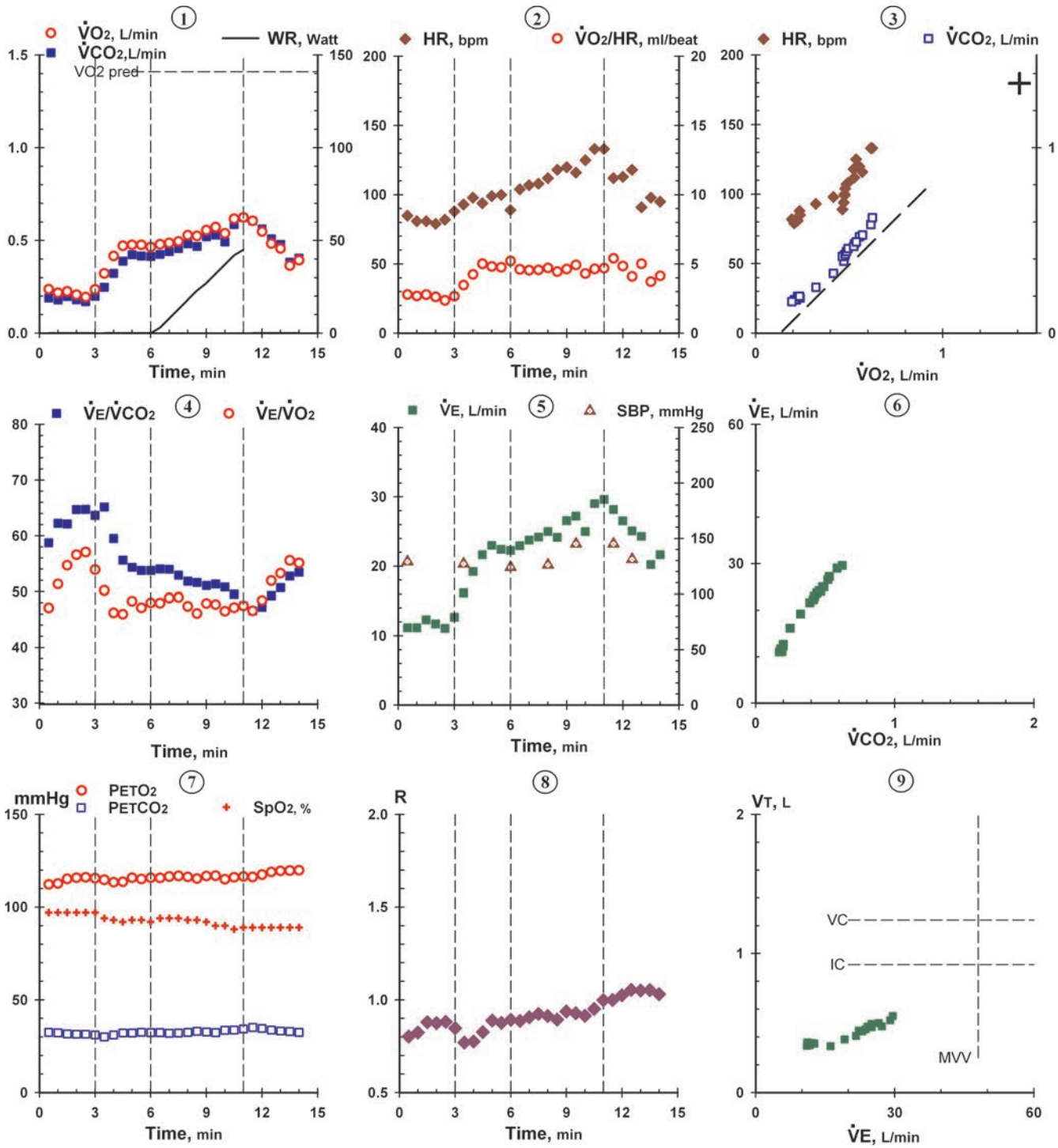

FIGURE 10.41.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $P_{ET}CO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

shallow breathing pattern contributed to an elevated effective V_D/V_T, which manifests as high ratios of $\dot{V}_E/\dot{V}CO_2$, although V:Q mismatch within the lung was probably also present. Despite the high $\dot{V}_E$ values and restricted lung mechanics, there appeared to be an adequate breathing reserve. The findings are thus more consistent with limitation due to impaired cardiovascular response, evident soon after the onset of exercise, rather than limitation by the mechanics of breathing.

Conclusion

Analysis indicates that the patient has severely impaired exercise capacity consistent with pulmonary vascular disease secondary to CREST syndrome.

Table 10.41.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	129/72	85	31	11.2	0.19	0.24	2.8	0.80			112			32			59	47	
1.0	Rest		81	32	11.1	0.18	0.22	2.7	0.82			113			32			62	51	
1.5	Rest		81	35	12.3	0.20	0.23	2.8	0.88			115			32			62	55	
2.0	Rest		79	34	11.7	0.18	0.21	2.6	0.87			116			31			65	57	
2.5	Rest		82	33	11.1	0.17	0.19	2.4	0.88			116			32			65	57	
3.0	Unloaded		88	36	12.7	0.20	0.24	2.7	0.85			116			31			64	54	
3.5	Unloaded	127/73	93	49	16.2	0.25	0.32	3.5	0.77			115			30			65	50	
4.0	Unloaded		98	50	19.2	0.32	0.42	4.2	0.78			113			31			60	46	
4.5	Unloaded		94	53	21.6	0.39	0.47	5.0	0.83			114			32			56	46	
5.0	Unloaded		99	52	23.0	0.42	0.48	4.8	0.89			116			32			54	48	
5.5	Unloaded		100	51	22.4	0.42	0.48	4.8	0.88			115			33			54	47	
6.0	Unloaded	124/74	89	50	22.3	0.41	0.46	5.2	0.89			116			32			54	48	
6.5	3		104	52	23.0	0.43	0.48	4.6	0.89			116			32			54	48	
7.0	8		107	52	23.8	0.44	0.49	4.5	0.91			116			32			54	49	
7.5	13		108	51	24.2	0.46	0.49	4.6	0.93			117			32			53	49	
8.0	18	126/84	112	53	25.0	0.48	0.53	4.7	0.91			116			32			52	47	
8.5	23		118	51	24.2	0.47	0.52	4.4	0.89			115			33			52	46	
9.0	27		120	53	26.6	0.52	0.56	4.6	0.94			117			33			51	48	
9.5	32	145/81	116	57	27.2	0.53	0.57	4.9	0.93			117			32			51	48	
10.0	37		125	51	25.0	0.49	0.54	4.3	0.91			115			34			51	46	
10.5	42		133	56	29.0	0.59	0.62	4.6	0.95			116			34			50	47	
11.0	45		133	54	29.6	0.62	0.62	4.7	1.00			117			34			48	47	
11.5	Recovery	145/81	112	53	28.2	0.61	0.61	5.4	1.00			116			35			47	47	
12.0	Recovery		113	52	26.5	0.56	0.55	4.8	1.03			118			35			47	48	
12.5	Recovery	131/93	118	51	25.1	0.51	0.48	4.1	1.05			119			34			49	52	
13.0	Recovery		91	53	24.3	0.48	0.46	5.0	1.05			120			33			51	53	
13.5	Recovery		98	47	20.2	0.38	0.36	3.7	1.05			120			33			53	56	
14.0	Recovery		95	49	21.7	0.41	0.39	4.1	1.03			120			32			53	55	

Case 42 Severe Pulmonary Vascular Disease Secondary to Sarcoidosis: Air and Oxygen Breathing Studies

CLINICAL FINDINGS

This 29-year-old man with a 6-year history of sarcoidosis was referred for evaluation of worsening dyspnea. His condition was manifest in hilar lymphadenopathy, patchy interstitial infiltrates, which had improved with prior corticosteroid therapy, and pulmonary hypertension. He was on continuous O_2 supplementation and an inhaled corticosteroid, but he was no longer taking systemic corticosteroids. His weight was stable. He had a remote history of smoking cigarettes for 1 year.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer while breathing room air. After a period of rest, the test was repeated while breathing 100% O_2. On both occasions, he pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 10 W per minute to tolerance. Arterial blood was sampled every second minute, and intra-arterial pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of shortness of breath while breathing room air and because of leg fatigue while breathing O_2. The resting ECG showed right axis deviation and inverted T waves anteriorly. The T waves became upright during exercise. No arrhythmias were noted.

INTERPRETATION

Comments

Resting respiratory function studies showed mild-to-moderate restrictive and obstructive defects in ventilatory mechanics, an extremely low DLCO, and severe arterial hypoxemia (Tables 10.42.1 and 10.42.2).

Analysis

Referring to Flowchart 1 (Fig. 8.1), both the peak $\dot{V}O_2$ and anaerobic threshold were severely reduced (see Table 10.42.2). Proceeding to Flowchart 4 (Fig. 8.4) through branch point 4.1, the breathing reserve was normal, but the high $\dot{V}E/\dot{V}CO_2$ at the *AT* (branch point 4.3) and high VD/VT (branch point 4.2) (Table 10.42.3) led to the boxes representing lung disease with impaired oxygenation and abnormal pulmonary circulation. With O_2 breathing (Table 10.42.4 and Fig. 10.42.2), there was no evidence of a right-to-left shunt. However, the reversal of hypoxemia and reduction in ventilatory drive allowed the patient to tolerate a considerably higher work rate.

Conclusion

This patient had a mild-to-moderate disturbance in ventilatory mechanics but severe gas exchange abnormality due to pulmonary vascular disease. He had severe hypoxemia at rest and during exercise. Although supplemental oxygen reversed his hypoxemia and increased his work capacity somewhat, exercise impairment remained severe.

Table 10.42.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		29
Sex		Male
Height (cm)		171
Weight (kg)	73	58
Hematocrit (%)		45
VC (L)	4.28	3.11
IC (L)	2.85	1.59
TLC (L)	5.82	4.78
FEV_1 (L)	3.46	2.27
FEV_1/VC (%)	81	73
MVV (L/min)	138	91
DLCO (mL/mm Hg/min)	29.9	6.9

Table 10.42.2

Selected Exercise Data

Measured	Predicted	Measurement	
		Air	100% O_2
Maximum work rate (W)		40	70
Peak $\dot{V}O_2$ (L/min)	2.64	0.8	
Maximum heart rate (beats/min)	191	149	150
Maximum O_2 pulse (mL/beat)	13.6	5.7	
AT (L/min)	>1.08	0.7	
Blood pressure (mm Hg [rest, max ex])		114/72, 135/78	111/69, 141/87
Maximum $\dot{V}E$ (L/min)		64	70
Exercise breathing reserve (L/min)	>15	27	21
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	24.9	61.8	63.5
PaO_2 (mm Hg [rest,max ex])		42, 35	585, 605
$P(A-a)O_2$ (mm Hg [rest, max ex])		52, 74	84, 57
$PaCO_2$ (mm Hg [rest, max ex])		46, 45	44, 51
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		16, 22	19, 28
V_D/V_T (rest, max ex)		0.57, 0.67	0.63, 0.71
HCO_3^- (mEq/L [rest, 2-min recov])		27, 24	25, 24

Table 10.42.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	*a*	*(A − a)*	*ET*	*a*	*(a − ET)*			
	Rest	111/66								7.39	27		41			45				
0.5	Rest		96	18	15.6	0.27	0.34	3.5	0.79			113			30			52	41	
1.0	Rest		93	19	15.8	0.26	0.32	3.4	0.81			114			29			55	44	
1.5	Rest		95	19	16.1	0.26	0.31	3.3	0.84			116			28			56	47	
2.0	Rest		92	18	14.3	0.25	0.30	3.3	0.83			114			29			51	43	
2.5	Rest	114/72	93	20	16.3	0.28	0.36	3.9	0.78	7.38	27	111	42	52	30	46	16	52	41	0.57
3.0	Rest		94	23	20.6	0.41	0.54	5.7	0.76			112			30			45	35	
3.5	Unloaded		108	29	19.2	0.31	0.34	3.1	0.91			116			29			54	49	
4.0	Unloaded		114	31	31.0	0.50	0.57	5.0	0.88			119			26			57	50	
4.5	Unloaded		120	30	33.0	0.52	0.55	4.6	0.95			120			26			59	55	
5.0	Unloaded		122	32	36.5	0.56	0.60	4.9	0.93			119			28			60	56	
5.5	Unloaded		123	32	39.1	0.60	0.61	5.0	0.98			122			26			61	60	
6.0	Unloaded	116/72	123	35	42.5	0.65	0.66	5.4	0.98	7.38	26	122	37	67	26	45	19	61	60	0.64
6.5	10		125	36	45.1	0.68	0.69	5.5	0.99			123			25			62	61	
7.0	10		129	38	45.8	0.69	0.69	5.3	1.00			122			27			62	62	
7.5	20		130	39	54.4	0.81	0.78	6.0	1.04			125			24			63	65	
8.0	20	129/78	131	37	51.7	0.77	0.73	5.6	1.05	7.37	26	126	35	72	23	45	22	63	67	0.65
8.5	30		140	41	57.4	0.82	0.77	5.5	1.06			126			24			66	70	
9.0	30		140	44	63.3	0.88	0.80	5.7	1.10			127			24			68	74	
9.5	40	135/78	145	43	63.6	0.89	0.79	5.4	1.13	7.35	24	127	35	74	23	45	22	67	76	0.67
10.0	Recovery		149	48	63.0	0.89	0.80	5.4	1.11			129			22			66	74	
10.5	Recovery		140	39	56.3	0.81	0.72	5.1	1.13			126			25			65	74	
11.0	Recovery		140	36	50.5	0.80	0.79	5.6	1.01			122			26			59	60	
11.5	Recovery		138	34	50.1	0.75	0.70	5.1	1.07			123			25			63	67	
12.0	Recovery	114/69	133	39	52.5	0.77	0.74	5.6	1.04	7.33	24	122	35	70	28	46	18	64	66	0.66

Table 10.42.4

Oxygen Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest									7.34	25		519			47				
0.5	Rest		67	21	20.6	0.29									24			65		
1.0	Rest		63	21	16.0	0.24									27			59		
1.5	Rest		58	19	17.2	0.23									25			68		
2.0	Rest	111/69	59	18	16.7	0.24				7.36	24		585	84	25	44	19	62		0.63
2.5	Rest		66	18	14.4	0.18									25			72		
3.0	Rest		64	20	17.1	0.23									25			67		
3.5	Unloaded		90	23	25.9	0.36									23			67		
4.0	Unloaded		93	28	26.0	0.37									25			64		
4.5	Unloaded		90	23	24.6	0.34									23			67		
5.0	Unloaded		95	25	28.4	0.40									25			66		
5.5	Unloaded		93	25	29.8	0.42									24			66		
6.0	Unloaded	116/75	94	24	28.6	0.41				7.35	25		615	52	25	46	21	65		0.66
6.5	10		92	26	33.1	0.46									25			67		
7.0	10		100	27	30.9	0.44									27			65		
7.5	20		103	29	35.8	0.52									26			64		
8.0	20	120/78	108	27	38.1	0.56				7.33	25		620	44	26	49	23	64		0.68
8.5	30		110	31	38.6	0.56									26			64		
9.0	30		114	28	40.6	0.60									26			64		
9.5	40		123	35	50.6	0.73									26			65		
10.0	40	132/81	125	34	50.8	0.75				7.31	25		612	51	26	50	24	64		0.69
10.5	50		132	34	52.5	0.79									27			63		
11.0	50		140	43	62.8	0.87									24			68		
11.5	60		150	40	63.5	0.91									25			66		
12.0	60	141/87	150	47	69.9	0.96				7.28	24		605	57	23	51	28	68		0.71
12.5	Recovery		133	40	57.6	0.83									25			65		
13.0	Recovery		112	31	42.1	0.82									31			48		

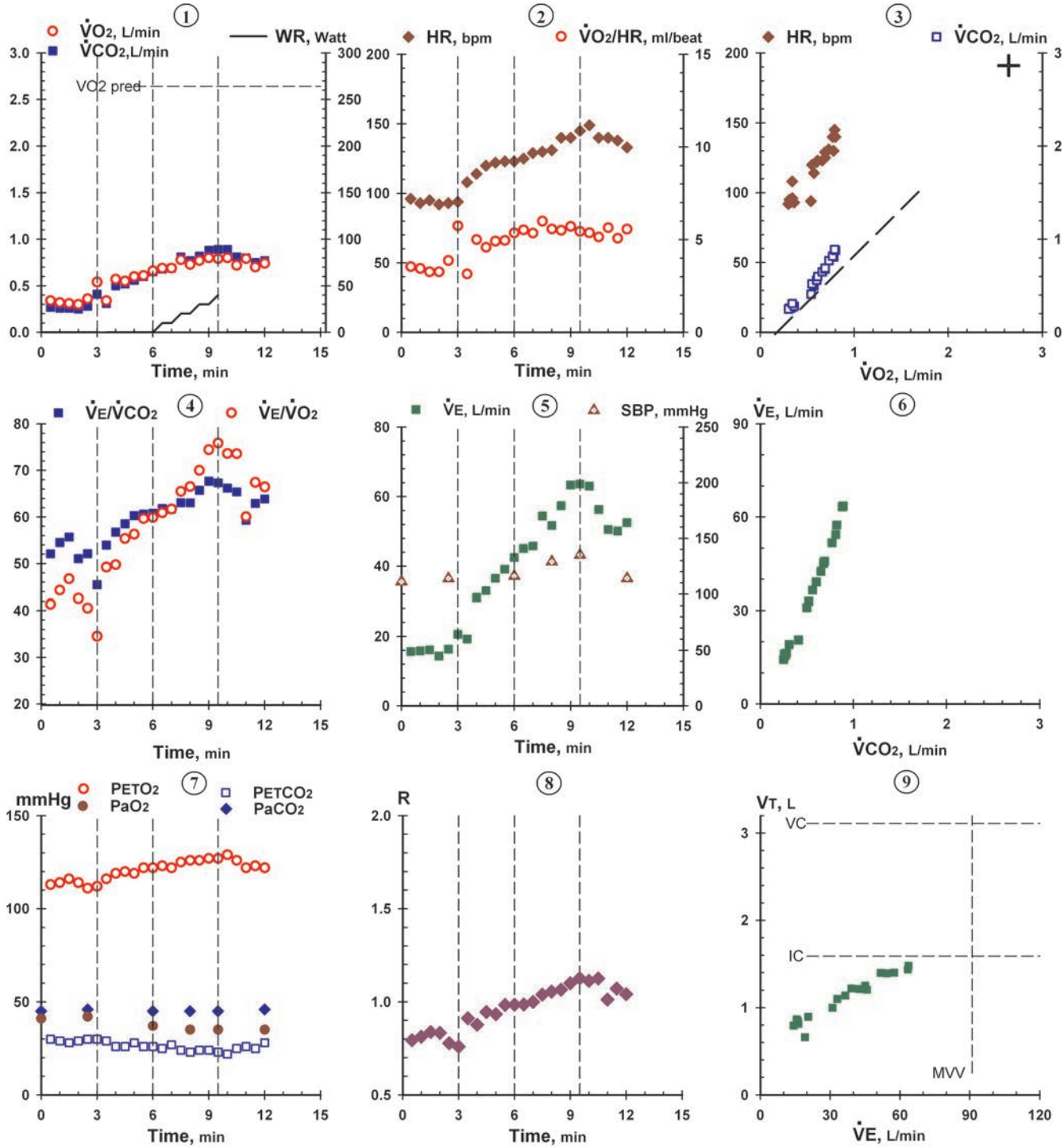

FIGURE 10.42.1. Air breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

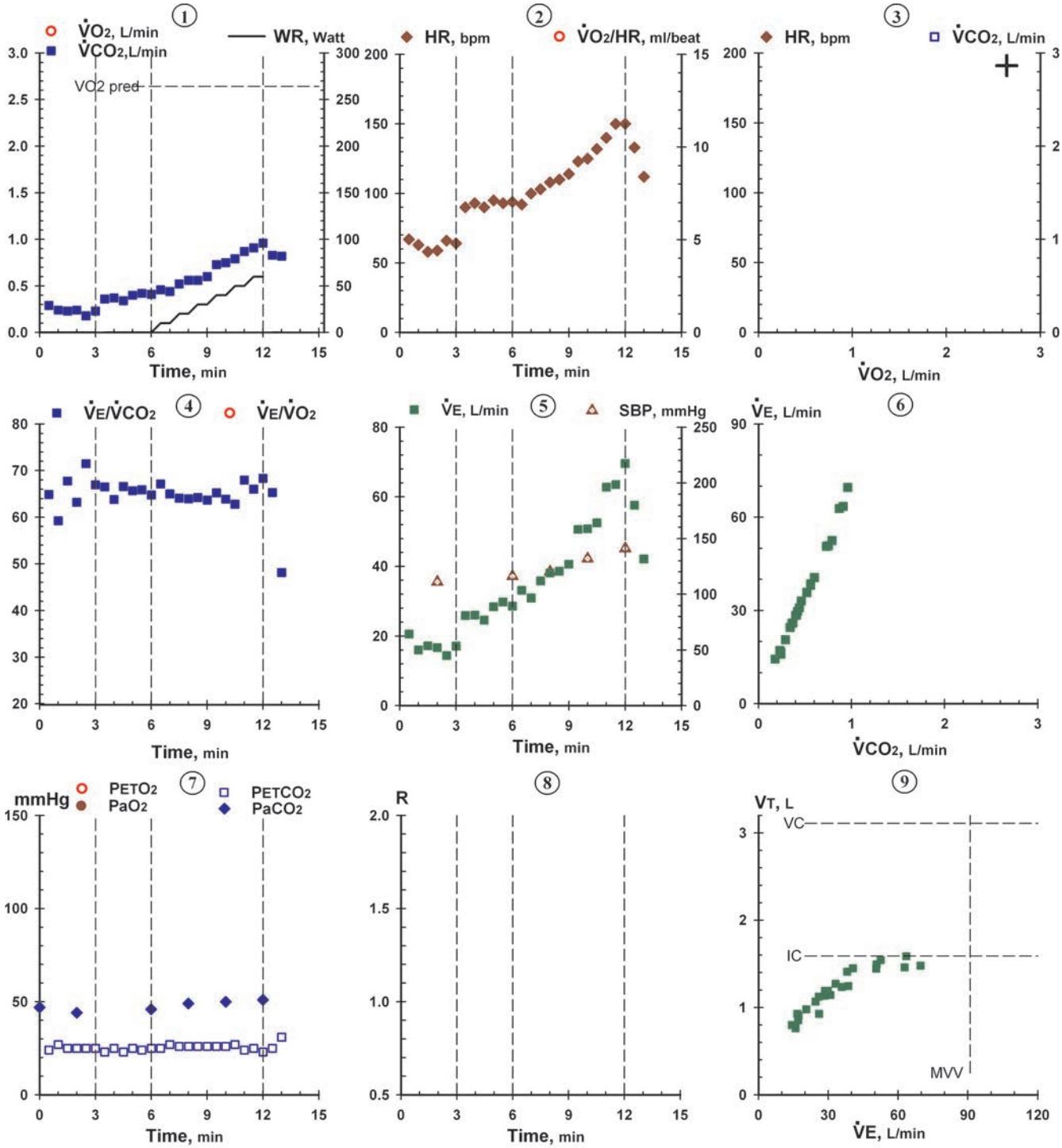

FIGURE 10.42.2. Oxygen breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate the beginning of unloaded cycling, the start of increasing work rate at 10 W per minute, and the start of recovery. Oxygen uptake data are not shown because of technical limitations of calculation with very high-inspired oxygen levels.

Case 43 Exercise-Induced Pulmonary Hypertension Secondary to Left Ventricular Diastolic Dysfunction

CLINICAL FINDINGS

This 67-year-old woman presented with 2 years of exertional dyspnea. She was previously quite physically active and first noted symptoms during her regular dance classes. She eventually discontinued dancing due to progressive dyspnea but continued to be as active as her symptoms would allow. By the time of this evaluation, she was short of breath walking on a level grade. She monitored her heart rate while active and reported that she was severely short of breath when her heart rate rose above 120 to 130 bpm, requiring that she stop to rest and recover before resuming activities. She had no symptoms at rest. She was a lifelong nonsmoker and had a stable weight. Her medical history was significant for hypothyroidism well managed on levothyroxine, and osteoporosis treated with alendronate sodium. Physical examination and chest radiographs were normal. An ECG showed a right bundle branch block. An echocardiogram obtained 1 year prior to evaluation had shown normal left ventricular function (ejection fraction 65% to 70%), mild mitral regurgitation, and aortic sclerosis without stenosis. There was no evidence of pulmonary hypertension, but mild-to-moderate diastolic dysfunction by transmitral flow indices was noted.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer beginning with 3 minutes of pedaling at 60 rpm without added load, followed by continuous increase in work rate of 10 W per minute until she stopped due to leg fatigue, marked dyspnea, and an inability to maintain a cadence above 40 rpm. There were no arrhythmias or ischemic changes on ECG.

INTERPRETATION

Comments

The pulmonary function tests were normal (Table 10.43.1).

Analysis

The peak $\dot{V}O_2$ was low normal and *AT* was at or below the lower limit of normal. The O_2 pulse at peak exercise was also lower than the predicted value (Tables 10.43.2 and 10.43.3). These findings could be consistent with either below-average fitness or early cardiovascular dysfunction. Because she had a history of an active lifestyle, the latter was suspected. Perhaps consistent with this, the $\Delta\dot{V}O_2/\Delta WR$ slope appeared lower than normal. This was a somewhat equivocal finding, however, as the $\dot{V}O_2$ increased excessively during the initial minutes of cycling due to some difficulty with smooth pedaling, which caused some distortion of the subsequent slope. There were no arrhythmias or repolarization abnormalities to suggest myocardial ischemia as the basis for these findings. With

Table 10.43.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		67
Sex		Female
Height (cm)		157
Weight (kg)		60
Hematocrit (%)		39.4
VC (L)	2.67	3.02
IC (L)	1.78	2.33
FEV_1 (L)	2.13	2.26
FEV_1/VC (%)	83	75
MVV (L/min)	98	90

Table 10.43.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.16	1.08
Maximum heart rate (beats/min)	153	157
Maximum O_2 pulse (mL/beat)	7.6	6.9
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	
AT (L/min)	>0.64	0.60
Blood pressure (mm Hg [rest, max])		107/90, 182/115
Maximum $\dot{V}E$ (L/min)		56
Exercise breathing reserve (L/min)	>15	34
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	30.4	33.2

respect to ventilation, there was a large breathing reserve, indicating that she was not limited by lung mechanics. The ventilatory equivalents decreased during exercise; however, the values remained above average at the *AT*. This finding, along with the low anaerobic threshold and probably abnormal $\Delta\dot{V}O_2/\Delta WR$, raised the question of a pulmonary vascular abnormality. Diastolic dysfunction, which had been identified on her prior echocardiogram, could account for exertional symptoms, the abnormalities in the $\dot{V}O_2$ response to exercise, and the above-average ventilatory equivalents. Based on this suspicion, a right heart catheterization was performed for measurement of central vascular pressures at rest and during exercise. At rest, pulmonary capillary wedge pressure was normal at 8 mm Hg. Immediately after a brief period of arm exercise (raising and lowering both arms holding a 1 L saline bag in each hand), however, the pulmonary capillary wedge pressure increased markedly to 24 mm Hg. The exercise-induced pulmonary venous hypertension was attributed to impaired diastolic relaxation of the left ventricle and was the probable basis of her exertional symptoms.

Conclusion

Although this patient's peak $\dot{V}O_2$ was in the normal range, it was below average and the anaerobic threshold was low. These findings, in the context of the clinical history, raised suspicion for early cardiovascular disease. This was further supported by the finding of borderline values for ventilatory equivalents. Exercise-induced pulmonary venous hypertension due to diastolic dysfunction was confirmed on follow-up cardiac catheterization.

Table 10.43.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	*a*	(*A* − *a*)	*ET*	*a*	(*a* − *ET*)			
0																				
0.5	Rest	107/90	103	19	12.0	0.30	0.29	2.8	1.04			117			32			40	41	
1.0	Rest		104	23	10.8	0.24	0.27	2.6	0.88			110			35			46	41	
1.5	Rest		95	20	13.2	0.36	0.38	4.0	0.95			113			34			37	35	
2.0	Rest		99	21	10.7	0.26	0.28	2.8	0.95			112			35			41	39	
2.5	Rest	130/89	102	21	11.8	0.30	0.32	3.1	0.95			113			34			39	37	
3.0	Rest		102	22	11.5	0.30	0.32	3.1	0.96			113			35			38	36	
3.5	Unloaded	130/89	104	24	14.8	0.38	0.41	4.0	0.92			110			36			39	36	
4.0	Unloaded		121	31	21.5	0.58	0.64	5.3	0.91			112			34			37	34	
4.5	Unloaded		126	32	20.4	0.57	0.60	4.8	0.95			112			35			36	34	
5.0	Unloaded		122	34	25.8	0.72	0.71	5.8	1.02			116			33			36	36	
5.5	Unloaded	154/96	127	29	22.2	0.66	0.68	5.4	0.97			112			36			33	32	
6.0	Unloaded		130	25	24.3	0.75	0.73	5.6	1.02			113			36			33	33	
6.5	3		122	32	23.6	0.68	0.64	5.3	1.05			115			35			35	37	
7.0	8		120	25	21.4	0.66	0.66	5.5	1.01			113			36			32	33	
7.5	13		121	26	21.0	0.62	0.63	5.2	0.98			111			36			34	33	
8.0	18		120	26	22.8	0.68	0.66	5.5	1.03			115			35			34	35	
8.5	23	156/107	126	23	17.7	0.55	0.60	4.8	0.91			107			38			32	29	
9.0	27		131	28	27.3	0.81	0.81	6.2	1.00			114			35			34	34	
9.5	33		133	29	29.4	0.87	0.79	6.0	1.10			118			33			34	37	
10.0	37		133	24	27.2	0.80	0.71	5.4	1.13			119			32			34	38	
10.5	42		135	30	30.3	0.86	0.78	5.7	1.11			119			31			35	39	
11.0	48	161/115	140	29	28.5	0.85	0.80	5.7	1.07			117			33			34	36	
11.5	52		142	26	32.4	0.96	0.85	6.0	1.12			119			32			34	38	
12.0	57		145	25	32.6	1.00	0.89	6.2	1.12			118			33			33	37	
12.5	62		147	39	37.4	1.03	0.88	6.0	1.17			122			30			36	43	
13.0	67		150	39	42.3	1.16	1.01	6.7	1.15			121			30			36	42	
13.5	72	182/85	153	30	40.4	1.15	0.95	6.2	1.22			122			31			35	43	
14.0	77		155	38	48.3	1.26	1.06	6.8	1.19			123			29			38	46	
14.5	82		157	48	55.8	1.34	1.08	6.9	1.24			126			27			42	52	
15.0	Recovery	182/85	156	58	56.0	1.21	0.97	6.2	1.25			128			25			46	58	
15.5	Recovery		154	43	44.2	1.04	0.81	5.3	1.29			127			26			42	55	
16.0	Recovery		147	47	47.0	0.93	0.60	4.1	1.55			133			22			51	78	
16.5	Recovery		131	51	39.1	0.69	0.45	3.4	1.53			134			21			57	87	

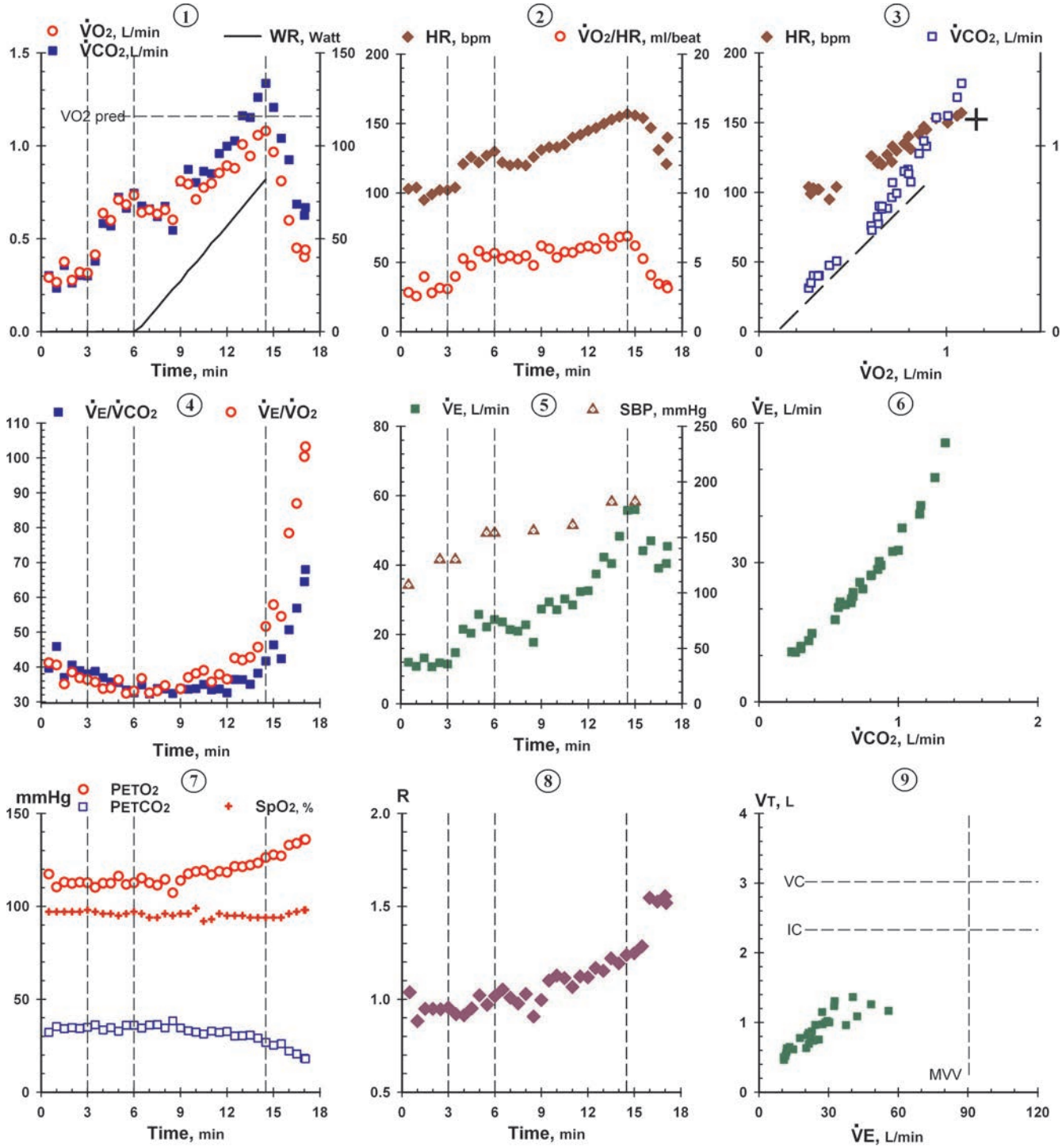

FIGURE 10.43.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 44 Intrapulmonary Right-to-Left Shunt due to Pulmonary Arteriovenous Fistulae

CLINICAL FINDINGS

This 26-year-old man had multiple pulmonary arteriovenous malformations (AVMs) and recurrent brain abscesses. He was referred for exercise testing to assess his functional status before undergoing embolization of the pulmonary AVMs. He denied shortness of breath and, until recently, had worked as an aerobics instructor. The patient was normally developed and thin but muscular. He had no rales or murmurs on examination of the chest, but had marked cyanosis and clubbing of the fingers. A recent study while the patient was seated at rest breathing oxygen reported an estimated right-to-left shunt of 53%.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased continuously at a rate of 20 W per minute to tolerance. Blood was sampled every second minute, and intra-arterial pressure was recorded from a percutaneously placed brachial artery catheter. Heart rate and rhythm were continuously monitored; 12-lead ECGs were obtained during rest, exercise, and recovery. The patient appeared to give an excellent effort and stopped exercise because of general and leg fatigue without dyspnea or chest pain. No arrhythmias or ischemic changes were noted on ECG.

INTERPRETATION

Comments

Resting respiratory function studies showed a mild restrictive defect (Table 10.44.1). Hemoglobin concentration was elevated and resting arterial blood analysis showed hypoxemia and a chronic respiratory alkalosis.

Analysis

The most striking findings of the test were severe hypoxemia, low P_{ETCO_2}, and high V_D/V_T, which are characteristic of pulmonary vascular disease (Table 10.44.2 and Fig. 10.44.1). Although pulmonary AVMs are reasonably categorized as pulmonary vascular disease, this patient's condition differed from most other cases of pulmonary vascular disease. That is, he had severe chronic hypoxemia with secondary erythrocytosis in the absence of primary heart or lung disease, and had large right-to-left shunt in the absence of pulmonary hypertension. The hypoxemia was similar in degree to that of patients with large right-to-left shunt due to congenital heart disease but without the structural cardiac defects. Interestingly, the combined effect of the patient's low saturation and secondary erythrocytosis resulted in an arterial O_2 content that was near normal (see Table 10.44.3). This suggests that hypoxemia did not fully account for the patient's low peak $\dot{V}O_2$ and *AT* (Table 10.44.2).

A unique aspect of this patient's physiology is the presence of right-to-left shunting with an otherwise (presumably) normal pulmonary vascular circuit. This is in contrast to Eisenmenger syndrome in which right-to-left shunt only occurs after development of diffuse obliterative pulmonary vascular disease causing systemic level pulmonary vascular resistance and reversal of a previous left-to-right shunt. The gas exchange abnormalities in Eisenmenger result both from pulmonary V:Q mismatching due to diffuse pulmonary vascular occlusive disease (as in Cases 31 and 32 of this chapter) and from effects of the shunt. In this case, in contrast, gas exchange abnormalities are likely attributable to the shunt per se,

Table 10.44.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		26
Sex		Male
Height (cm)		189
Weight (kg)	87	64
Hemoglobin (g/100 mL)		21.8
VC (L)	5.55	4.18
IC (L)	3.70	2.94
FEV_1 (L)	4.50	3.95
FEV_1/VC (%)	81	94
MVV (L/min)		
Direct	183	169
Indirect	180	158

Table 10.44.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	3.12	2.19
Maximum heart rate (beats/min)	194	160
Maximum O_2 pulse (mL/beat)	16.1	13.7
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	9.9
AT (L/min)	>1.28	1.1
Blood pressure (mm Hg [rest, max])		144/84, 180/90
Maximum $\dot{V}E$ (L/min)		123
Exercise breathing reserve (L/min)	>15	35
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	23.9	43.5
SaO_2 (% [rest, max ex])		76, 64
PaO_2 (mm Hg [rest, max ex])		39, 39
$P(A-a)O_2$ (mm Hg [rest, max ex])		74, 76
$PaCO_2$ (mm Hg [rest, max ex])		32, 38
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		9, 15
VD/VT (rest, max ex)		0.42, 0.52
HCO_3^- (mEq/L [rest, 2-min recov])		22, 16

without significant contribution from pulmonary V:Q mismatching in the remainder of the pulmonary circulation. The high VD/VT and corresponding elevation in $\dot{V}E/\dot{V}CO_2$ (Table 10.44.3) in this case resulted from overventilation of alveoli that were perfused with pulmonary blood flow to compensate for the venous CO_2 shunted into the arterial circulation. Calculation of VD/VT by the modified Bohr equation (see Appendix C) compares the concentration of PCO_2 in exhaled breath to the concentration of PCO_2 in arterial blood and attributes the difference to regions of the lung with higher ventilation than perfusion. A right-to-left shunt is associated with exhaled PCO_2 concentrations that are lower than arterial due to compensatory ventilation of the nonshunt blood and therefore results in high calculated VD/VT. This patient's exercise $PaCO_2$ was around 35 mm Hg, but the pulmonary capillary PCO_2 had to have been much lower. This is also reflected in $P(a-ET)CO_2$, which increased from 9 mm Hg at rest to 15 mm Hg at max exercise (Fig. 10.44.1, panel 7). The calculated VD/VT was correspondingly increased (see Table 10.44.3).

Conclusion

The patient had a large right-to-left shunt because of pulmonary AVMs. The high VD/VT and positive $P(a-ET)CO_2$ values reflect the relative inefficiency of ventilation for removing CO_2 from the blood, consistent with a portion of right ventricular output bypassing the alveolar capillaries. In this patient, the wide $P(A-a)O_2$, positive $P(a-ET)CO_2$, and high VD/VT reflect the effects of shunting rather than the maldistribution of ventilation typical of more common lung diseases.

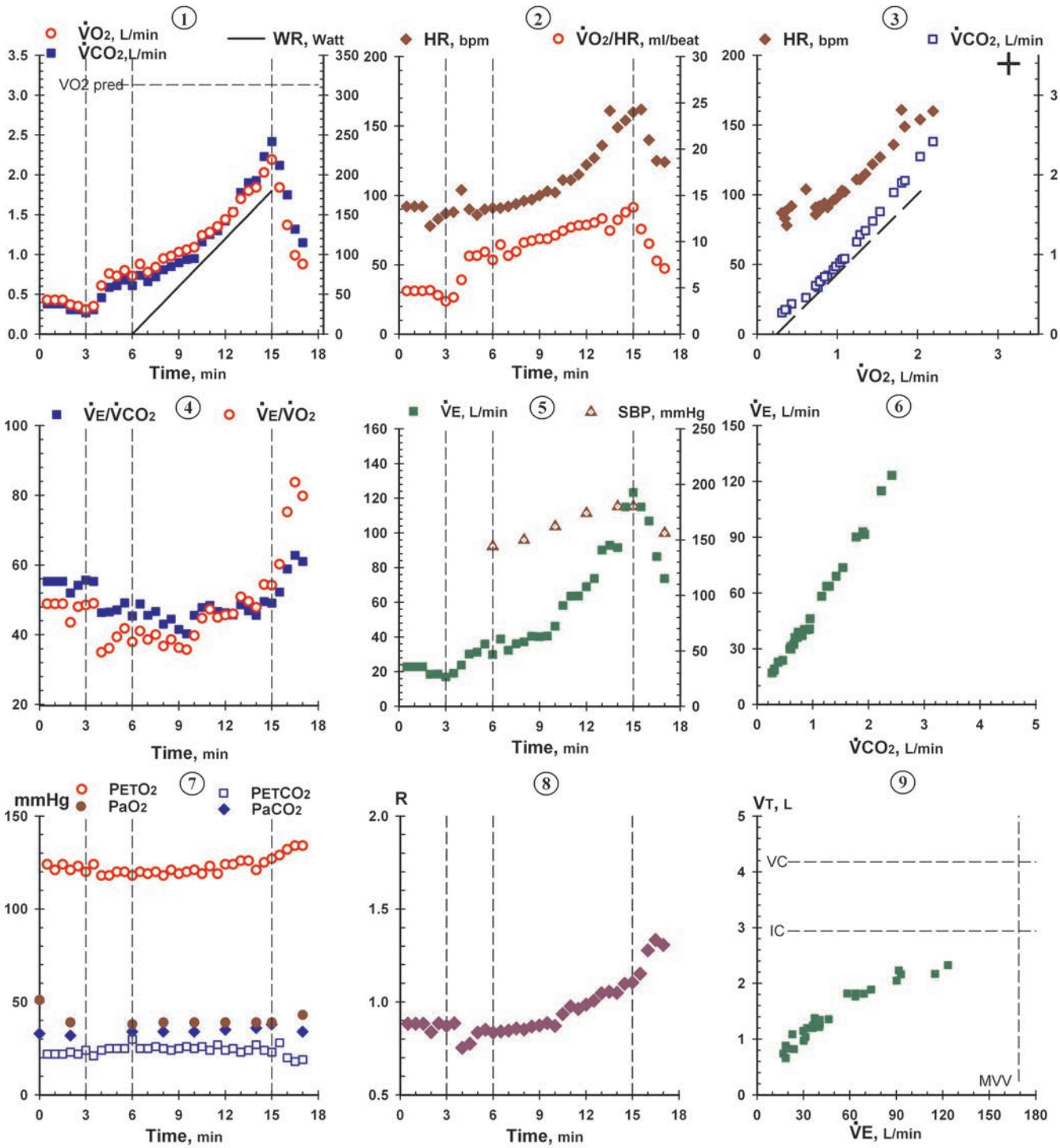

FIGURE 10.44.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.44.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	*a*	*(A − a)*	*ET*	*a*	*(a − ET)*			
	Rest									7.43	22		51			33				
0.5	Rest		92	21	22.8	0.38	0.43	4.7	0.88			124			22			55	49	
1.0	Rest		92	21	22.8	0.38	0.43	4.7	0.88			121			22			55	49	
1.5	Rest		92	21	22.8	0.38	0.43	4.7	0.88			124			22			55	49	
2.0	Rest		78	28	18.5	0.31	0.37	4.7	0.84	7.45	22	121	39	74	23	32	9	52	44	0.42
2.5	Rest		83	21	18.6	0.31	0.35	4.2	0.89			123			22			54	48	
3.0	Rest		87	23	17.0	0.27	0.31	3.6	0.87			120			24			56	49	
3.5	Unloaded		88	23	19.1	0.31	0.35	4.0	0.89			124			21			55	49	
4.0	Unloaded		104	29	23.8	0.46	0.61	5.9	0.75			118			24			46	35	
4.5	Unloaded		90	31	30.1	0.59	0.76	8.4	0.78			118			25			47	36	
5.0	Unloaded		86	30	31.3	0.61	0.73	8.5	0.84			120			25			47	39	
5.5	Unloaded		90	30	36.0	0.68	0.80	8.9	0.85			120			25			49	42	
6.0	Unloaded	144/84	91	26	26.9	0.61	0.73	8.0	0.84	7.43	22	118	38	73	30	34	4	45	38	0.41
6.5	10		91	31	38.8	0.74	0.88	9.7	0.84			120			25			49	41	
7.0	20		92	27	32.4	0.66	0.78	8.5	0.85			119			25			46	39	
7.5	30		94	29	36.1	0.72	0.84	8.9	0.86			120			26			47	40	
8.0	40	150/90	96	27	37.2	0.81	0.95	9.9	0.85	7.42	22	118	39	72	25	34	9	43	37	0.39
8.5	50		97	30	40.4	0.85	0.98	10.1	0.87			121			24			45	39	
9.0	60		100	33	40.2	0.90	1.03	10.3	0.87			119			25			42	36	
9.5	70		103	32	40.6	0.94	1.06	10.3	0.89			120			26			40	36	
10.0	80	162/90	102	34	46.2	0.95	1.09	10.7	0.87	7.42	22	121	39	73	25	34	9	46	40	0.42
10.5	90		111	32	58.2	1.16	1.24	11.2	0.94			119			26			48	45	
11.0	100		111	36	63.6	1.25	1.28	11.5	0.98			123			24			48	47	
11.5	110		115	35	63.7	1.30	1.35	11.7	0.96			119			27			47	45	
12.0	120	174/96	122	38	69.0	1.42	1.44	11.8	0.99	7.38	20	124	39	76	24	35	11	46	46	0.45
12.5	130		127	39	73.7	1.54	1.53	12.0	1.01			124			25			46	46	
13.0	140		136	44	90.2	1.76	1.70	12.5	1.05			126			23			49	51	
13.5	150		161	43	92.9	1.90	1.80	11.2	1.06			126			24			47	50	
14.0	160	180/90	149	41	91.5	1.93	1.84	12.3	1.05	7.36	20	121	39	76	27	36	9	46	48	0.46
14.5	170		154	53	115.0	2.23	2.03	13.2	1.10			125			24			50	54	
15.0	180	180/96	160	53	123.3	2.42	2.19	13.7	1.11	7.31	19	127	39	76	23	38	15	49	54	0.52
15.5	Recovery		162	49	115.0	2.12	1.84	11.4	1.15			129			28			52	60	
16.0	Recovery		140	45	106.9	1.75	1.37	9.8	1.28			132			20			59	75	
16.5	Recovery		125	41	86.4	1.32	0.99	7.9	1.33			134			18			63	84	
17.0	Recovery	156/84	124	41	73.7	1.15	0.88	7.1	1.31	7.30	16	134	43	79	19	34	15	61	80	0.56

Case 45 Mild Chronic Bronchitis with Normal Exercise Performance

CLINICAL FINDINGS

This 55-year-old shipyard worker complained of dyspnea after walking up one flight of stairs or a few blocks on a level surface. He had morning cough several months of each year and had noted occasional retrosternal pain unrelated to exertion or emotional upset. He had 35 pack-years of smoking until stopping 12 years ago. He exercised regularly. The physical examination was normal except for mild obesity. Chest radiographs showed bilateral pleural thickening in the midlung zones and areas of old granulomatous disease. Resting ECG was normal.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He first pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 20 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of "exhaustion." The ECG remained normal throughout exercise.

Table 10.45.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		54
Sex		Male
Height (cm)		174
Weight (kg)	77	88
Hematocrit (%)		45
VC (L)	4.28	3.59
IC (L)	2.86	3.12
TLC (L)	6.38	6.15
FEV_1 (L)	3.39	2.40
FEV_1/VC (%)	79	67
MVV (L/min)	142	112
D_{LCO} (mL/mm Hg/min)	28.8	29.8

INTERPRETATION

Comments

Resting respiratory function was compatible with mild airflow obstruction (Table 10.45.1). The resting ECG was normal.

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and anaerobic threshold were normal (Table 10.45.2 and Fig. 10.45.1). Referring to Flowchart 2 (Fig. 8.2), arterial blood gases (Table 10.45.3) and ECG at peak $\dot{V}O_2$ were

Table 10.45.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.42	2.66
Maximum heart rate (beats/min)	166	169
Maximum O_2 pulse (mL/beat)	14.6	15.7
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	9.9
AT (L/min)	>1.04	1.3
Blood pressure (mm Hg [rest, max])		144/93, 225/117
Maximum $\dot{V}E$ (L/min)		86
Exercise breathing reserve (L/min)	>15	26
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.4	26.7
PaO_2 (mm Hg [rest, max ex])		81, 92
$P(A-a)O_2$ (mm Hg [rest, max ex])		18, 21
$PaCO_2$ (mm Hg [rest, max ex])		43, 40
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		5, –3
V_D/V_T (rest, heavy ex)		0.41, 0.23
HCO_3^- (mEq/L [rest, 2-min recov])		26, 16

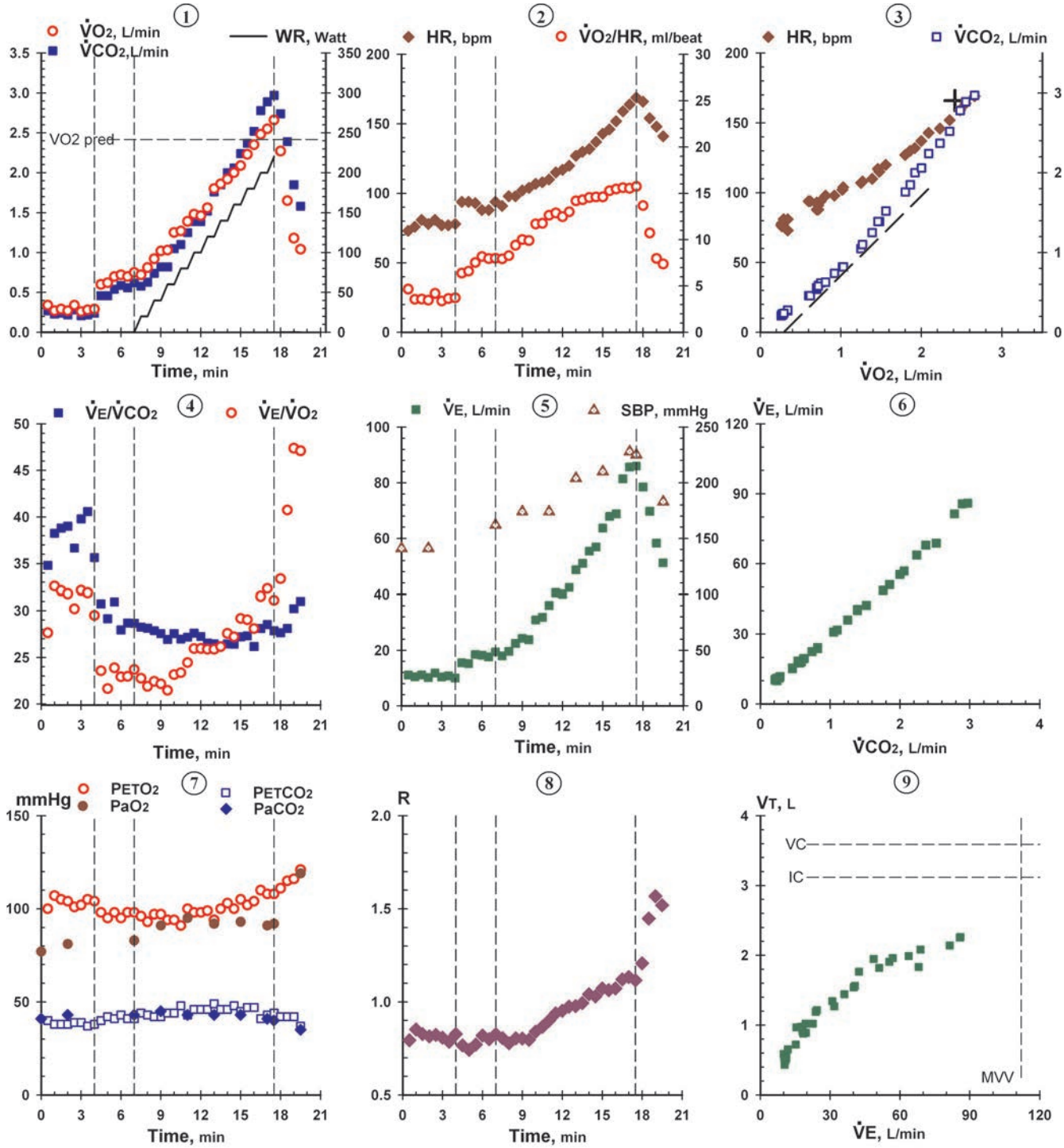

FIGURE 10.45.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

normal (branch point 2.1). The patient was about 14% overweight (branch point 2.2). Although obesity was not severe, it did contribute to the additional metabolic cost of work. The patient also had mild airflow obstruction, which was evident in resting pulmonary function tests and in expiratory airflow patterns at high exercise levels. Because the patient had normal ventilatory equivalents, the mild reduction in ventilatory capacity did not result in his exhausting the exercise breathing reserve; there was thus no evidence of ventilatory limitation to exercise.

Conclusion

This study illustrates normal exercise performance in a man with mild chronic obstructive pulmonary disease.

Table 10.45.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	141/93								7.42	26		77			41				
1.0	Rest		73	20	11.1	0.27	0.34	4.7	0.79			100			40			35	28	
1.5	Rest		76	20	10.5	0.23	0.27	3.6	0.85			107			38			38	33	
2.0	Rest		81	21	11.1	0.24	0.29	3.6	0.83			105			38			39	32	
2.5	Rest	144/90	78	19	10.2	0.22	0.27	3.5	0.81	7.40	26	104	81	18	38	43	5	39	32	0.41
3.0	Rest		81	18	11.8	0.28	0.34	4.2	0.82			101			39			37	30	
3.5	Rest		77	24	10.4	0.21	0.26	3.4	0.81			102			39			40	32	
4.0	Rest		77	22	10.8	0.22	0.28	3.6	0.79			105			37			41	32	
4.5	Rest		78	17	10.0	0.24	0.29	3.7	0.83			104			38			36	30	
5.0	Unloaded		94	16	15.5	0.46	0.60	6.4	0.77			98			40			31	24	
5.5	Unloaded		94	21	15.2	0.46	0.62	6.6	0.74			95			42			29	22	
6.0	Unloaded		93	21	18.5	0.54	0.70	7.5	0.77			98			41			31	24	
6.5	Unloaded		88	20	18.2	0.59	0.72	8.2	0.82			95			43			28	23	
7.0	Unloaded		88	18	17.6	0.56	0.70	8.0	0.80			98			41			29	23	
7.5	Unloaded	162/99	94	19	19.4	0.62	0.75	8.0	0.83	7.39	26	98	83	17	41	43	2	29	24	0.28
8.0	20		91	19	18.0	0.58	0.72	7.9	0.81			96			44			28	23	
8.5	20		98	22	19.6	0.63	0.81	8.3	0.78			93			43			28	22	
9.0	40		98	22	22.5	0.74	0.92	9.4	0.80			97			42			28	22	
9.5	40	174/96	102	20	24.3	0.82	1.02	10.0	0.80	7.37	26	97	91	5	42	45	3	28	22	0.28
10.0	60		104	20	23.8	0.82	1.03	9.9	0.80			94			44			27	21	
10.5	60		107	23	30.9	1.05	1.25	11.7	0.84			94			44			28	23	
11.0	80		108	25	31.8	1.10	1.27	11.8	0.87			91			48			27	23	
11.5	80	174/93	110	25	36.1	1.25	1.39	12.6	0.90	7.37	24	100	95	8	43	43	0	27	24	0.25
12.0	100		115	26	40.6	1.39	1.48	12.9	0.94			98			46			28	26	
12.5	100		117	26	40.1	1.39	1.46	12.5	0.95			98			46			27	26	
13.0	120		120	24	42.4	1.52	1.56	13.0	0.97			99			46			27	26	
13.5	120	204/99	127	25	48.7	1.76	1.80	14.2	0.98	7.36	24	94	92	14	49	43	–6	26	26	0.23
14.0	140		130	28	51.0	1.85	1.86	14.3	0.99			100			46			26	26	
14.5	140		132	29	55.4	2.00	1.92	14.5	1.04			103			46			26	28	
15.0	160		137	29	56.9	2.06	2.00	14.6	1.03			100			48			26	27	
15.5	160	210/105	143	32	63.7	2.24	2.09	14.6	1.07	7.35	23	105	93	16	45	43	–2	27	29	0.25
16.0	180		146	37	67.9	2.37	2.23	15.3	1.06			102			47			27	29	
16.5	180		152	33	68.8	2.52	2.35	15.5	1.07			104			47			26	28	
17.0	200		159	38	81.4	2.78	2.48	15.6	1.12			110			41			28	32	
17.5	200	228/114	164	38	85.7	2.89	2.55	15.5	1.13	7.33	21	108	91	22	43	41	–2	29	32	0.25
18.0	220	225/117	169	38	86.0	2.97	2.66	15.7	1.12	7.31	20	108	92	21	44	40	–4	28	31	0.22
18.5	Recovery		166	32	78.5	2.74	2.27	13.7	1.21			111			42			28	33	
19.0	Recovery		154	29	69.7	2.39	1.65	10.7	1.45			115			42			28	41	
19.5	Recovery		148	28	58.3	1.85	1.18	8.0	1.57			116			42			30	47	
20.0	Recovery	183/96	141	26	51.2	1.58	1.04	7.4	1.52	7.27	16	121	119	5	37	35	–2	31	47	0.20

Case 46 Emphysema with Mild Airway Obstruction

CLINICAL FINDINGS

This 50-year-old male, long-term smoker was referred for cardiopulmonary exercise testing for evaluation of his exertional dyspnea. He became symptomatic after walking one block. He had mild obstructive lung disease of long duration consistent with emphysema. His only medication was an inhaled β-agonist, which he used frequently.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 15 W per minute to tolerance. Heart rate and rhythm were continuously monitored; 12-lead ECGs were obtained during rest, exercise, and recovery. Blood pressure was measured with a sphygmomanometer, and oxygen saturation was monitored with a pulse oximeter (data not plotted). The patient appeared to give an excellent effort and stopped exercise because of shortness of breath. He denied chest pain during or after the study. Resting, exercise, and recovery ECGs were not remarkable except for occasional multifocal premature ventricular contractions during exercise and recovery.

Table 10.46.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		50
Sex		Male
Height (cm)		168
Weight (kg)	72	66
Hematocrit (%)		46
VC (L)	4.06	4.10
IC (L)	2.71	3.30
TLC (L)	5.92	7.07
FEV_1 (L)	3.22	2.57
FEV_1/VC (%)	79	63
MVV (L/min)	141	91
DLCO (mL/mm Hg/min)	25.4	14.7

INTERPRETATION

Comments

Resting respiratory function studies showed mild obstruction, an insignificant bronchodilator response to inhaled β-agonist, and a moderately reduced DLCO (Table 10.46.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ and the anaerobic threshold are low (Table 10.46.2). Going next to Flowchart 4 (Fig. 8.4), the breathing reserve (branch point 4.1) is very low, consistent with exercise limitation from lung disease. Although blood gases were not measured, the very high ventilatory equivalents, without a high R that would indicate acute hyperventilation (Fig. 10.46.1 and Table 10.46.3), likely reflect increased dead space ventilation (branch point 4.2). The low *AT* further augmented ventilatory requirements at the higher work rates. As a result, the patient required an inordinately high level of ventilation for a given level of exercise. The SaO_2 estimated from oximetry decreased during exercise (see Table 10.46.2),

Table 10.46.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.22	1.39
Maximum heart rate (beats/min)	170	126
Maximum O_2 pulse (mL/beat)	13.1	11.0
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	7.3
AT (L/min)	>0.95	0.9
Blood pressure (mm Hg [rest, max])		120/80, 160/100
Maximum $\dot{V}E$ (L/min)		89
Exercise breathing reserve (L/min)	>15	2
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.2	53.3
O_2 saturation (oximeter) (rest, max)		93, 88

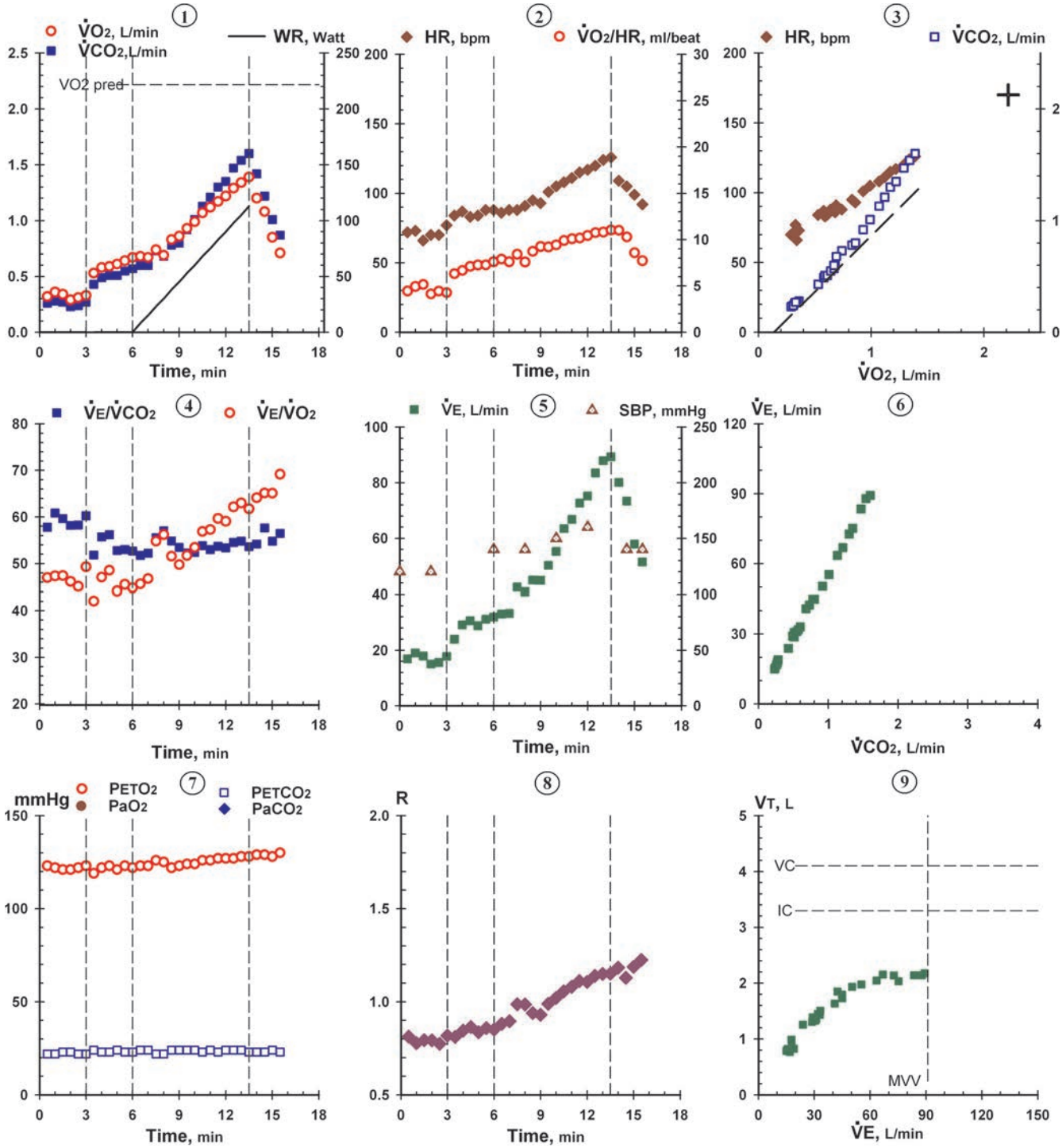

FIGURE 10.46.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

which may also have contributed to ventilatory drive. The heart rate reserve was high, consistent with ventilation limiting exercise prior to attainment of maximal cardiovascular stress. The low $\Delta\dot{V}O_2/\Delta WR$ might be due to pulmonary vascular disease secondary to the patient's obstructive lung disease or to reduced venous return during exercise, resulting from high intrathoracic pressure consequent to air trapping and hyperinflation.

Conclusion

This patient had only mild-to-moderate obstructive lung disease on resting pulmonary function tests. He nevertheless demonstrated ventilatory limitation to exercise due to the increased ventilatory requirements resulting from ventilation–perfusion mismatching and low *AT*.

Table 10.46.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	*a*	$(A-a)$	*ET*	*a*	$(a-ET)$			
	Rest	120/80																		
0.5	Rest		72	22	16.9	0.26	0.32	4.4	0.81			123			22			58	47	
1.0	Rest		73	23	19.0	0.28	0.36	4.9	0.78			122			22			61	47	
1.5	Rest		66	21	17.9	0.27	0.34	5.2	0.79			121			23			60	47	
2.0	Rest	120/80	70	19	15.0	0.23	0.29	4.1	0.79			121			23			58	46	
2.5	Rest		70	19	15.6	0.24	0.31	4.4	0.77			122			22			58	45	
3.0	Rest		77	18	17.8	0.27	0.33	4.3	0.82			123			22			60	49	
3.5	Unloaded		84	19	23.9	0.43	0.53	6.3	0.81			119			24			52	42	
4.0	Unloaded		87	21	29.1	0.49	0.58	6.7	0.84			122			23			56	47	
4.5	Unloaded		83	23	30.6	0.51	0.59	7.1	0.86			123			23			56	49	
5.0	Unloaded		84	22	28.8	0.51	0.61	7.3	0.84			121			24			53	44	
5.5	Unloaded		88	23	31.1	0.55	0.64	7.3	0.86			123			23			53	46	
6.0	Unloaded	140/90	88	22	31.9	0.57	0.67	7.6	0.85			122			23			53	25	
6.5	8		86	23	33.0	0.60	0.68	7.9	0.88			123			24			52	46	
7.0	15		88	22	33.2	0.60	0.67	7.6	0.90			123			24			52	47	
7.5	23		88	23	42.5	0.73	0.74	8.4	0.99			126			22			56	55	
8.0	30	140/90	91	25	40.9	0.68	0.69	7.6	0.99			125			22			57	56	
8.5	38		95	26	45.0	0.78	0.83	8.7	0.94			122			24			55	52	
9.0	45		93	25	44.9	0.80	0.86	9.2	0.93			123			24			53	50	
9.5	53		101	26	50.3	0.92	0.93	9.2	0.99			124			24			52	52	
10.0	60	150/92	105	28	55.3	1.01	0.99	9.4	1.02			124			24			52	53	
10.5	68		108	31	63.5	1.13	1.07	9.9	1.06			126			23			54	57	
11.0	75		111	31	66.8	1.21	1.12	10.1	1.08			126			24			53	57	
11.5	83		115	34	72.7	1.30	1.17	10.2	1.11			127			23			54	60	
12.0	90	160/100	117	37	75.2	1.35	1.22	10.4	1.11			127			24			53	59	
12.5	98		120	39	83.5	1.47	1.29	10.8	1.14			127			24			55	62	
13.0	105		124	41	87.9	1.54	1.34	10.8	1.15			128			24			55	63	
13.5	113		126	41	89.3	1.60	1.39	11.0	1.15			128			23			54	62	
14.0	Recovery		109	37	80.1	1.42	1.20	11.0	1.18			129			23			54	64	
14.5	Recovery	140/90	105	36	73.4	1.22	1.08	10.3	1.13			129			23			58	65	
15.0	Recovery		99	30	57.9	1.01	0.85	8.6	1.19			128			24			55	65	
15.5	Recovery	140/80	92	28	51.5	0.87	0.71	7.7	1.23			130			23			56	69	

Case 47 Severe Emphysema

CLINICAL FINDINGS

This 65-year-old man had a long history of asbestos exposure and heavy cigarette smoking. He was being treated with aminophylline, inhaled bronchodilators, and supplemental oxygen. He was also receiving chlorothiazide for treatment of hypertension. He had stopped smoking 12 years previously. Resting ECG suggested left atrial enlargement. The question was raised with respect to the role of the patient's circulatory disease in his ventilatory impairment.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 1 minute. The work rate was then increased 10 W per minute to his symptom-limited maximum. Blood was sampled every second minute, and intra-arterial blood pressure was recorded from a brachial artery catheter. There were no abnormal ST-segment changes at rest or during exercise. He stopped exercise complaining of shortness of breath.

Table 10.47.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		65
Sex		Male
Height (cm)		170
Weight (kg)	74	99
Hematocrit (%)		53
VC (L)	3.72	2.17
IC (L)	2.48	1.31
TLC (L)	5.85	8.22
FEV_1 (L)	2.89	0.56
FEV_1/VC (%)	78	26
MVV (L/min)	123	31
D_{LCO} (mL/mm Hg/min)	25.1	13.2

INTERPRETATION

Comments

This patient clearly had evidence of very severe obstructive lung disease (Table 10.47.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ was reduced, whereas the anaerobic threshold was not reached (Fig. 10.47.1, panel 3), so was evidently above the lower limits of normal (Table 10.47.2), which

Table 10.47.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.11	0.90
Maximum heart rate (beats/min)	155	129
Maximum O_2 pulse (mL/beat)	13.6	7.0
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.9
AT (L/min)	>0.93	Not reached
Blood pressure (mm Hg [rest, max])		175/94, 256/138
Maximum $\dot{V}E$ (L/min)		28
Exercise breathing reserve (L/min)	>15	3
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.7	32.2
PaO_2 (mm Hg [rest, max ex])		56, 46
$P(A-a)O_2$ (mm Hg [rest, max ex])		39, 48
$PaCO_2$ (mm Hg [rest, max ex])		45, 50
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		4, 6
V_D/V_T (rest, heavy ex)		0.40, 0.41
HCO_3^-, (mEq/L [rest, 2-min recov])		28, 27

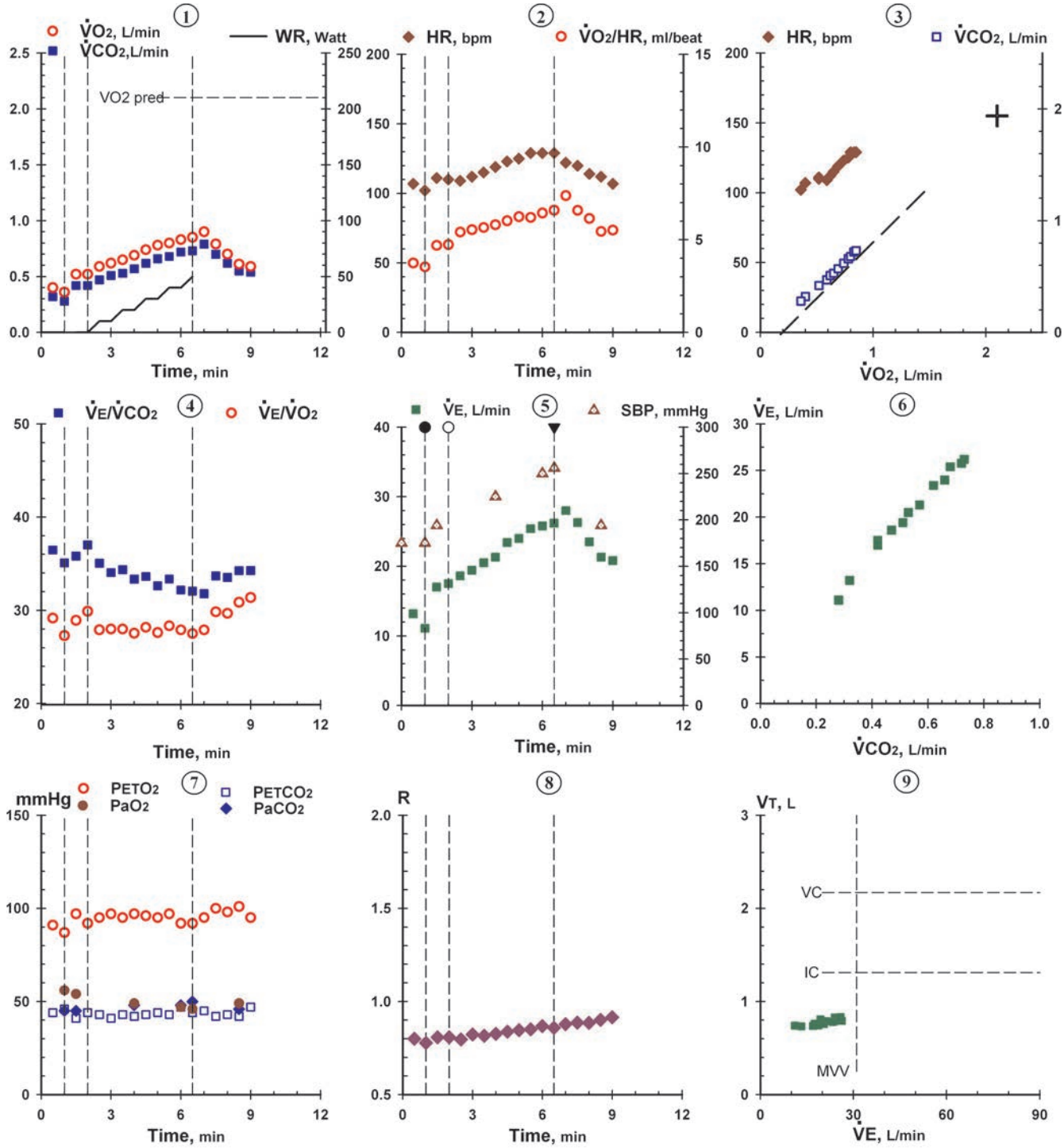

FIGURE 10.47.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

directs us through branch points 1.1, 1.2, and 1.3 to Flowchart 3 (Fig. 8.3). The breathing reserve was low (branch point 3.1), indicating exercise limitation due to lung disease, and consistent with this, there was evidence for ventilation–perfusion mismatching (increased V_D/V_T, $P[A-a]O_2$, and $P[a-ET]CO_2$) and a mild acute respiratory acidosis during exercise (Table 10.47.3). Although there was no breathing reserve at maximal exercise, there was a large heart rate reserve. The maximal breathing frequency was less than 50 (branch point 3.2), which is more typical of obstructive, as opposed to restrictive, lung disease. The increase in respiratory acidosis during exercise is also consistent with ventilatory limitation.

Conclusion

This patient with severe obstructive lung disease is presented to illustrate findings of ventilatory limitation. The heart rate reserve was high and breathing reserve was absent. Furthermore, he developed a mild acute respiratory acidosis at maximum $\dot{V}O_2$.

Table 10.47.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	PO_2, mm Hg			PCO_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	175/94																		
0.5	Rest		107	18	13.2	0.32	0.40	3.7	0.80			91			44			36	29	
1.0	Rest	175/94	102	15	11.1	0.28	0.36	3.5	0.78	7.41	28	87	56	39	46	45		35	27	0.40
1.5	Unloaded	194/100	111	23	17.0	0.42	0.52	4.7	0.81	7.41	28	97	54	43	41	45		36	29	0.41
2.0	Unloaded		110	23	17.5	0.42	0.52	4.7	0.81			92			44			37	30	
2.5	10		109	25	18.6	0.47	0.59	5.4	0.80			95			43			35	28	
3.0	10		112	24	19.4	0.51	0.62	5.5	0.82			97			41			34	28	
3.5	20		115	27	20.5	0.53	0.65	5.7	0.82			95			43			34	28	
4.0	20	225/113	119	27	21.3	0.57	0.69	5.8	0.83	7.40	29	97	49	45	42	48	6	33	28	0.41
4.5	30		123	30	23.4	0.62	0.74	6.0	0.84			96			43			34	28	
5.0	30		125	29	24.0	0.66	0.78	6.2	0.85			95			44			33	28	
5.5	40		129	32	25.4	0.68	0.80	6.2	0.85			97			43			33	28	
6.0	40	250/131	129	31	25.8	0.72	0.83	6.4	0.87	7.37	27	92	47	49	47	48	1	32	28	0.40
6.5	50	256/138	129	33	26.2	0.73	0.85	6.6	0.86	7.37	28	92	46	48	44	50	6	32	28	0.41
7.0	Recovery		122	34	28.0	0.79	0.90	7.4	0.88			95			45			32	28	
7.5	Recovery		120	32	26.3	0.70	0.79	6.6	0.89			100			42			34	30	
8.0	Recovery		114	32	23.5	0.62	0.70	6.1	0.89			98			43			34	30	
8.5	Recovery	194/94	112	29	21.3	0.55	0.61	5.4	0.90	7.38	27	101	49	51	42	46	4	34	31	0.40
9.0	Recovery		107	27	20.8	0.54	0.59	5.5	0.92			95			47			34	31	

Case 48 Emphysema with Pulmonary Vascular Disease

CLINICAL FINDINGS

This 61-year-old man with bullous emphysema was referred for evaluation regarding the need for oxygen supplementation. He had a 35 pack-year history of cigarette smoking. He had not sought medical care until 4 months previously, when he was hospitalized for pneumonia, severe dyspnea, and hemoptysis. No specific cause was found for his hemoptysis but he was found to have significant obstructive lung disease. A resting ECG showed poor R-wave progression.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 10 W per minute to tolerance. Arterial blood was sampled every second minute, and intra-arterial pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of leg fatigue. The patient had no chest pain or further ECG abnormalities.

INTERPRETATION

Comments

The patient was relatively thin (body mass index [BMI] 21). Resting pulmonary function tests showed a moderate obstructive ventilatory defect, increased total lung capacity, and low DLCO (Table 10.48.1).

Table 10.48.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		61
Sex		Male
Height (cm)		173
Weight (kg)	76	63
Hematocrit (%)		45
VC (L)	4.00	4.37
IC (L)	2.67	2.62
TLC (L)	6.15	9.11
FEV_1 (L)	3.13	2.11
FEV_1/VC (%)	78	48
MVV (L/min)	131	87
DLCO (mL/mm Hg/min)	26.0	8.4

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ and anaerobic threshold were decreased (Table 10.48.2). In Flowchart 4 (Fig. 8.4), the low breathing reserve (branch point 4.1) and high VD/VT (branch point 4.2) are consistent with lung disease. The high VT/IC and low breathing reserve support the conclusion of ventilatory limitation. Ventilatory drive was also increased due to a high VD/VT and the onset of lactic acidosis at a low work rate. Although the patient stated that he stopped exercise because of leg fatigue, the exhaustion of his breathing reserve indicates that he could not have exercised much further, and he was at or near ventilatory limitation. The abnormal gas exchange (high ventilatory equivalents at *AT*, high VD/VT, and positive $P[a - ET]CO_2$) with exercise was consistent with the presence of areas in

Table 10.48.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.95	1.25
Maximum heart rate (beats/min)	159	149
Maximum O_2 pulse (mL/beat)	12.3	8.4
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.5
AT (L/min)	>0.86	0.7
Blood pressure (mm Hg [rest, max])		127/75, 190/96
Maximum $\dot{V}E$ L/min		85
Exercise breathing reserve (L/min)	>15	2
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.2	38.0
PaO_2 (mm Hg [rest, max ex])		83, 72
$P(A - a)O_2$ (mm Hg [rest, max ex])		32, 52
$PaCO_2$ (mm Hg [rest, max ex])		36, 34
$P(a - ET)CO_2$ (mm Hg [rest, max ex])		4, 8
VD/VT (rest, max ex)		0.28, 0.41
HCO_3^- (mEq/L [rest, 2-min recov])		22, 13

Table 10.48.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
	Rest	129/75								7.44	22		86			33				
0.5	Rest		77	15	13.9	0.30	0.28	3.6	1.07			122			30			42	45	
1.0	Rest		75	13	10.8	0.23	0.23	3.1	1.00			121			31			42	42	
1.5	Rest		76	14	9.9	0.21	0.21	2.8	1.00			118			32			41	41	
2.0	Rest	129/75	75	15	10.8	0.27	0.26	3.5	1.04	7.41	22	118	83	32	32	36	4	35	37	0.28
2.5	Rest		74	12	10.4	0.22	0.20	2.7	1.10			123			29			43	47	
3.0	Rest		75	11	10.4	0.25	0.24	3.2	1.04			120			31			38	39	
3.5	Unloaded		83	20	17.8	0.40	0.38	4.6	1.05			117			32			40	42	
4.0	Unloaded	138/41	86	19	18.6	0.43	0.41	4.8	1.05	7.41	22	121	91	25	30	35	5	40	41	0.34
4.5	Unloaded		89	16	19.6	0.48	0.46	5.2	1.04			120			30			38	40	
5.0	Unloaded		94	17	21.2	0.52	0.51	5.4	1.02			120			31			38	39	
5.5	Unloaded		94	18	24.4	0.59	0.57	6.1	1.04			121			30			39	40	
6.0	Unloaded	168/90	95	18	25.0	0.62	0.59	6.2	1.05	7.40	21	121	78	38	30	35	5	38	40	0.33
6.5	10		97	17	25.3	0.64	0.59	6.1	1.08			120			31			37	40	
7.0	10	168/90	98	20	29.0	0.71	0.65	6.6	1.09	7.41	22	122	77	40	29	35	6	38	42	0.34
7.5	20		101	22	28.5	0.70	0.64	6.3	1.09			119			32			38	42	
8.0	20	174/90	102	21	32.5	0.78	0.70	6.9	1.11	7.40	21	123	74	45	29	34	5	39	44	0.34
8.5	30		104	24	28.9	0.73	0.67	6.4	1.09			120			32			37	40	
9.0	30	174/40	110	21	40.1	0.96	0.83	7.5	1.16	7.40	21	124	71	48	28	35	7	40	46	0.37
9.5	40		115	20	38.7	0.97	0.84	7.3	1.15			122			30			38	44	
10.0	40	180/90	119	23	44.4	1.08	0.92	7.7	1.17	7.39	20	123	71	49	29	34	5	39	46	0.34
10.5	50		123	22	47.7	1.16	0.95	7.7	1.22			125			28			40	48	
11.0	50	182/88	126	25	51.7	1.22	0.97	7.7	1.26	7.38	19	125	70	52	28	33	5	41	51	0.34
11.5	60		130	25	56.9	1.35	1.05	8.1	1.29			126			28			41	52	
12.0	60	189/93	132	26	58.7	1.40	1.08	8.2	1.30	7.36	18	125	72	51	29	33	4	40	52	0.34
12.5	70		138	26	62.3	1.47	1.12	8.1	1.31			127			28			41	54	
13.0	70	190/90	140	31	68.1	1.54	1.14	8.1	1.35	7.32	17	128	72	51	27	34	7	43	57	0.39
13.5	80		144	32	71.4	1.62	1.19	8.3	1.36			127			28			42	58	
14.0	80	190/96	149	38	80.2	1.73	1.24	8.3	1.40	7.32	17	129	72	52	26	34	8	44	62	0.41
14.5	90		148	39	85.2	1.80	1.25	8.4	1.44			129			26			45	66	
15.0	Recovery		141	27	66.6	1.49	1.07	7.6	1.39			129			26			43	60	
15.5	Recovery		140	26	63.3	1.38	0.90	6.4	1.53			130			26			44	68	
16.0	Recovery		133	22	54.5	1.19	0.74	5.6	1.61			131			26			44	71	
16.5	Recovery	174/87	126	22	51.3	1.07	0.65	5.2	1.65	7.26	13	132	115	14	25	30	5	46	76	0.36
17.0	Recovery		120	24	45.5	0.88	0.54	4.5	1.63			133			24			49	80	

the lungs of uneven matching of V:Q. This, along with low DLCO, is consistent with pulmonary vascular disease, presumably due to his obstructive lung disease. The severity of the metabolic acidosis (decrease in HCO_3^- from 22 to 13 mEq/L) was consistent with the low anaerobic threshold and suggests poor O_2 flow to the exercising muscle, which could result from pulmonary vascular disease, thus limiting his ability to increase cardiac output.

Conclusion

This patient had evidence of abnormal oxygen flow, which may result from secondary pulmonary vascular disease, coexistent systemic vascular disease, or reduction in skeletal muscle capacity for oxygen utilization, all commonly associated with obstructive lung disease. The degree of exercise hypoxemia was mild and would not likely to account for this. This case is presented as an example of the effects of cardiovascular dysfunction in patients with chronic lung disease. Lung disease frequently causes secondary cardiovascular impairment, which in turn raises ventilatory requirements by causing lactic acidosis at low levels of exercise. As a result, ventilatory limitation may be reached earlier than might be expected from the degree of abnormality on pulmonary function testing.

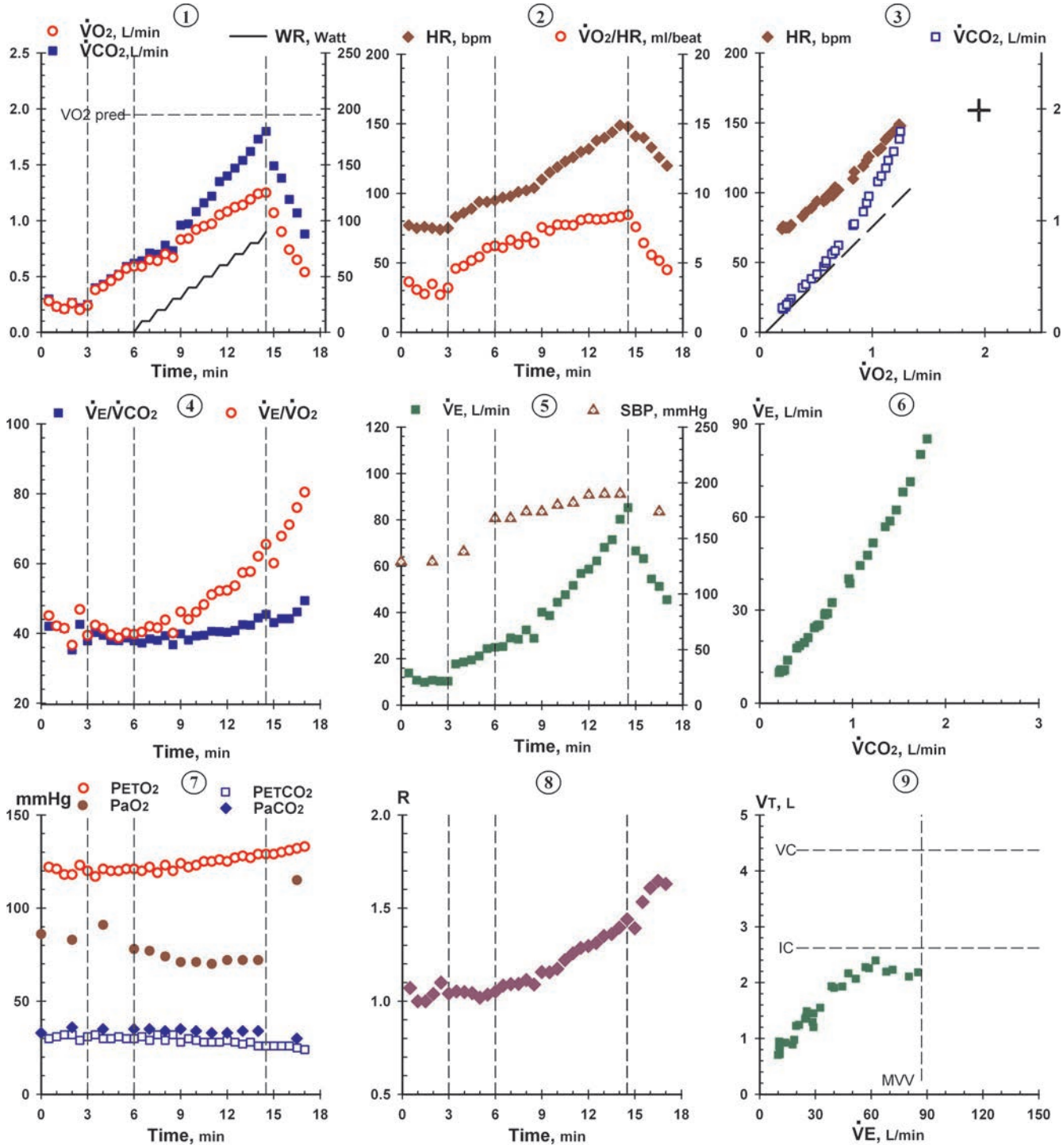

FIGURE 10.48.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 49 Severe Emphysema and Bronchitis: Air and Oxygen Breathing Studies

CLINICAL FINDINGS

This 62-year-old retired accountant had a long history of heavy cigarette smoking, which he had stopped 4 years previously. He had a chronic cough and shortness of breath. He had gradually increased his activity by physical training and rode his bicycle many miles daily. There was no history of heart disease. He took oral theophylline but no other medications. He participated in a study evaluating the effects of oxygen supplementation.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes while breathing humidified air. The work rate was then increased 10 W per minute to his symptom-limited maximum. Blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. He stopped exercise complaining of shortness of breath. Following 30 minutes of rest, he was given humidified 100% O_2 to breathe while the exercise study was repeated. He again stopped exercise complaining of shortness of breath. The 12-lead ECG showed no ST-segment changes or arrhythmia. While breathing 100% oxygen, the patient was able to exercise longer and attain a higher peak work rate.

Table 10.49.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		62
Sex		Male
Height (cm)		173
Weight (kg)	76	78
Hematocrit (%)		51
VC (L)	4.30	1.67
IC (L)	2.87	1.22
TLC (L)	6.87	8.30
FEV_1 (L)	3.40	0.54
FEV_1/VC (%)	79	32
MVV (L/min)	131	32
D_{LCO} (mL/mm Hg/min)	30.9	18.5

INTERPRETATION

Comments

Resting respiratory function studies indicated severe obstructive lung disease (Table 10.49.1). He also had significant systemic hypertension at rest (Table 10.49.2).

Table 10.49.2

Selected Exercise Data

Measurement	Predicted	Room air	100% O_2
Maximum WR (W)		80	120
Peak $\dot{V}O_2$ (L/min)	2.11	0.96	
Maximum heart rate (beats/min)	158	140	165
Maximum O_2 pulse (mL/beat)	13.4	6.9	
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.3	
AT (L/min)	>0.93	Not reached	
Blood pressure (mm Hg [rest, max])		169/106, 250/125	144/94, 234/119
Maximum $\dot{V}E$ (L/min)		32	40
Exercise breathing reserve (L/min)	>15	0	−8
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.3	28.5	23.2
PaO_2 (mm Hg [rest, max ex])		78, 53	587, 583
$P(A-a)O_2$ (mm Hg [rest, max ex])		21, 51	77, 66
$PaCO_2$, mm Hg (rest, max ex)		47, 53	49, 64
$P(a-ET)CO_2$, mm Hg (rest, max ex)		6, 5	8, 3
V_D/V_T (rest, heavy ex)		0.42, 0.38	0.48, 0.37
HCO_3^- (mEq/L [rest, 2-min recov])		25, 24	27, 22

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ was moderately to severely reduced and the anaerobic threshold was not reached (Table 10.49.2). Flowchart 3 (Fig. 8.3) could be used to analyze this case, but Flowchart 5 (Fig. 8.5) is more detailed. The indices of ventilation–perfusion mismatching (V_D/V_T, $P[a - ET]CO_2$, and $P[A - a]O_2$) were abnormal (branch point 5.1). The breathing reserve was zero (branch point 5.3), indicating exercise limitation due to lung disease. The breathing frequency (f) is less than 50 at the maximum work rate (branch point 5.7), consistent with obstructive lung disease. Other abnormal findings are an obstructive expiratory flow pattern (not shown), SaO_2 and $P(A - a)O_2$ that were borderline at rest and became abnormal with exercise, a high heart rate reserve, and an acute respiratory acidosis at end exercise (Table 10.49.3).

While breathing 100% O_2 (Fig. 10.49.2 and Table 10.49.4), the patient attained a maximal work rate that was 40 W higher and a maximum heart rate that was 25 bpm higher than during air breathing. These results demonstrated that the high heart rate reserve seen during the air breathing test resulted from his ventilatory limitation. Moreover, the maximum exercise ventilation increased from 32 L per minute (similar to his measured MVV) while breathing air to 40 L per minute while breathing oxygen.

The increased work rate achieved during O_2 breathing was due in part to depression of the ventilatory response to exercise, as evidenced by a greater degree of respiratory acidosis on the oxygen breathing test (increase in $PaCO_2$ of 6 mm Hg above rest during air breathing, as compared with 15 mm Hg for oxygen breathing). PaO_2 remained above 580 mm Hg when breathing oxygen (see Table 10.49.4),

Table 10.49.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest		107	20	9.7	0.23	0.24	2.2	0.96			99			44			35	33	
0.5	Rest		109	21	8.7	0.17	0.19	1.7	0.89			94			46			41	36	
1.0	Rest		108	20	8.8	0.19	0.21	1.9	0.90			98			44			37	34	
1.5	Rest		110	20	9.8	0.22	0.24	2.2	0.92			102			42			37	34	
2.0	Rest		112	20	8.4	0.16	0.18	1.6	0.89			103			41			42	37	
2.5	Rest	169/106	108	19	9.1	0.20	0.22	2.0	0.91	7.35	25	102	78	21	42	47	6	37	34	0.42
3.0	Unloaded		109	23	10.9	0.22	0.25	2.3	0.88			96			45			41	36	
3.5	Unloaded		111	25	13.4	0.31	0.37	3.3	0.84			97			44			36	30	
4.0	Unloaded		114	24	13.6	0.32	0.36	3.2	0.89			97			44			36	32	
4.5	Unloaded		121	23	14.2	0.35	0.40	3.3	0.88			96			45			35	31	
5.0	Unloaded		119	25	13.1	0.30	0.34	2.9	0.88			98			44			37	32	
5.5	Unloaded	181/100	117	24	15.3	0.39	0.44	3.8	0.89	7.35	27	99	71	25	43	49	6	34	30	0.42
6.0	10		119	24	14.4	0.36	0.41	3.4	0.88			98			44			34	30	
6.5	10		121	25	14.8	0.38	0.42	3.5	0.90			99			43			33	30	
7.0	20		121	24	15.1	0.37	0.41	3.4	0.90			98			44			35	32	
7.5	20	187/106	124	25	16.3	0.42	0.48	3.9	0.88	7.35	27	97	68	27	44	49	6	34	30	0.42
8.0	30		125	29	16.4	0.40	0.46	3.7	0.87			97			44			35	30	
8.5	30		128	22	18.6	0.56	0.64	5.0	0.88	7.35	27	94			46			30	26	
9.0	40		131	27	18.9	0.52	0.58	4.4	0.90			95			46			32	29	
9.5	40	213/113	130	24	21.1	0.64	0.72	5.5	0.89	7.35	26	94	61	36	47	48	1	30	26	0.36
10.0	50		132	27	21.9	0.66	0.72	5.5	0.92			96			46			30	27	
10.5	50		136	28	23.9	0.72	0.77	5.7	0.94			96			46			30	28	
11.0	60		137	30	25.0	0.77	0.82	6.0	0.94			96			47			29	27	
11.5	60	225/119	135	28	25.6	0.81	0.86	6.4	0.94	7.35	27	96	57	42	48	49	1	29	27	0.35
12.0	70		138	31	25.4	0.80	0.84	6.1	0.95			95			49			28	27	
12.5	70		138	32	29.0	0.91	0.94	6.8	0.97			95			48			29	28	
13.0	80		140	32	29.2	0.94	0.96	6.9	0.98			98			48			28	28	
13.5	80	250/125	124	37	32.1	1.02	0.85	6.9	1.20	7.32	27	101	53	51	48	53	5	28	34	0.38
14.0	Recovery		104	32	30.7	0.99	0.95	9.1	1.04			99			48			28	29	
14.5	Recovery		102	26	25.2	0.83	0.79	7.7	1.05			98			50			28	29	
15.0	Recovery		114	24	21.3	0.66	0.61	5.4	1.08			101			48			29	32	
15.5	Recovery		102	22	17.8	0.52	0.47	4.6	1.11	7.30	24	103	89	15	47	50	3	31	34	0.39

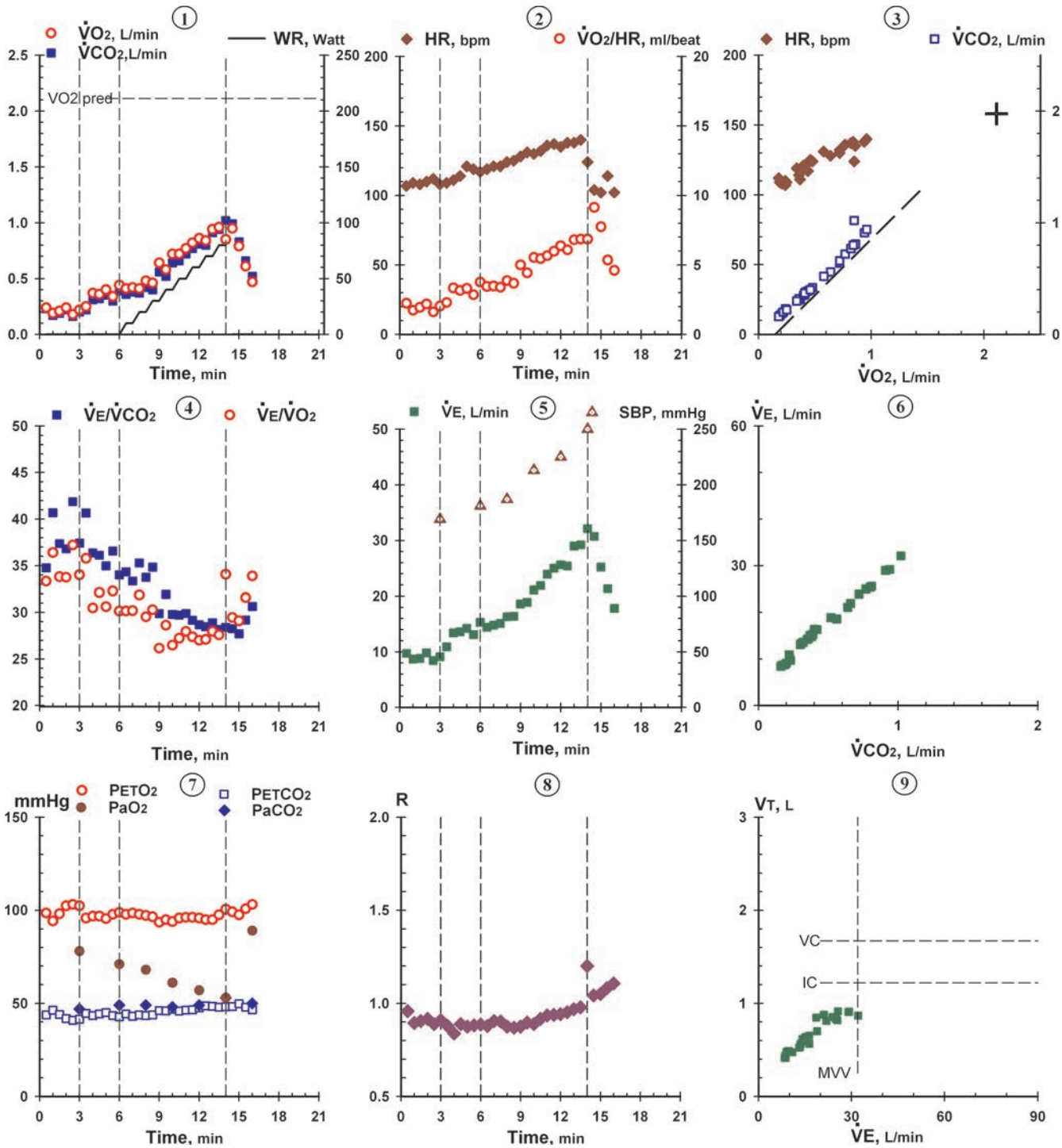

FIGURE 10.49.1. Air breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

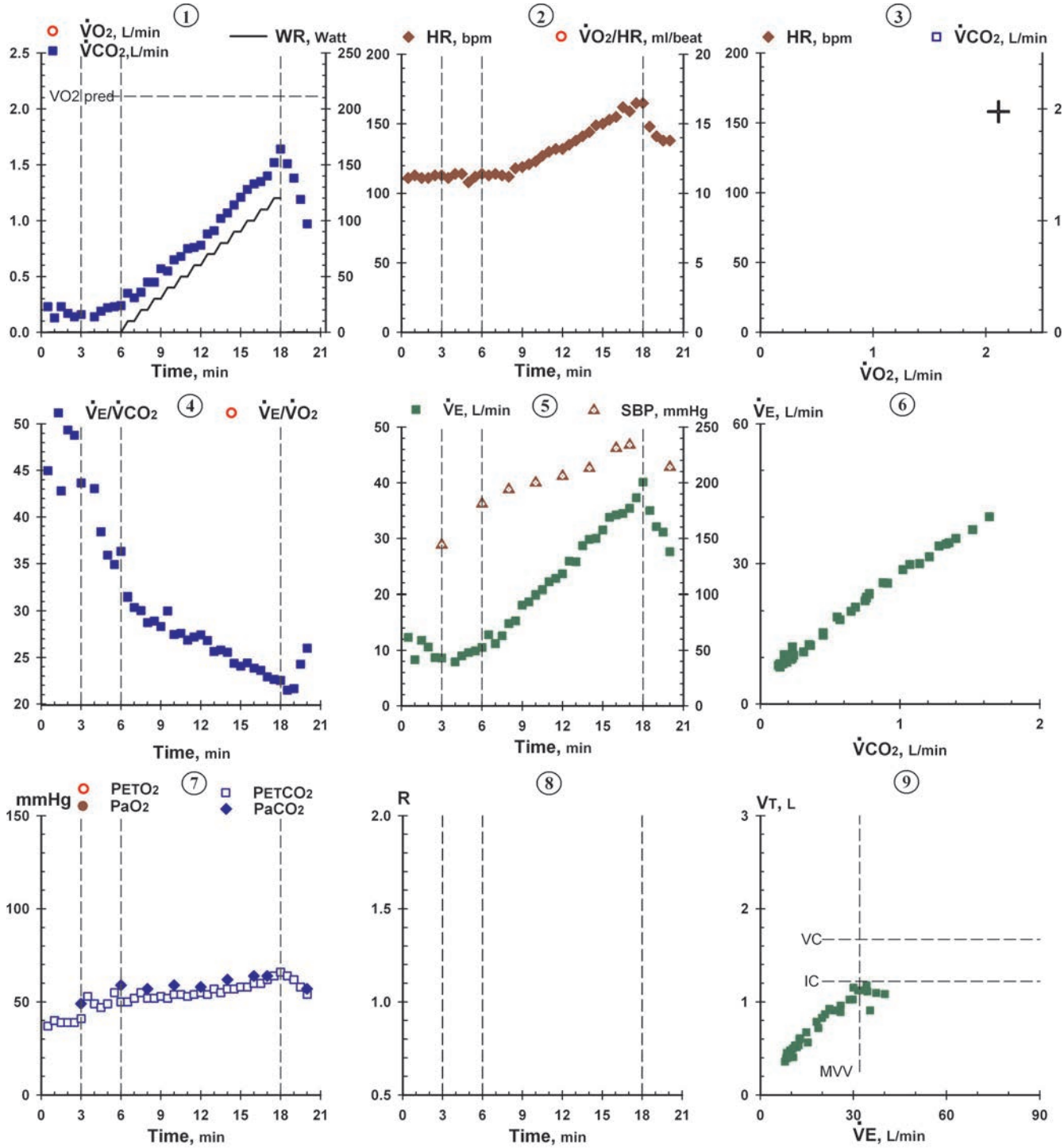

FIGURE 10.49.2. Oxygen breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, the start of increasing work rate at 10 W per minute, and the start of recovery. Oxygen uptake data are not shown because of technical limitations of calculations with very high-inspired oxygen levels.

Table 10.49.4

Oxygen Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest		111	23	12.3	0.23									37			45		
0.5	Rest		113	21	8.3	0.13									40			50		
1.0	Rest		111	23	11.8	0.23									39			43		
1.5	Rest		111	26	10.6	0.17									39			49		
2.0	Rest		113	22	8.7	0.14									39			49		
2.5	Rest	144/94	113	19	8.6	0.16				7.35	27		587	77	41	49	8	44		0.48
3.0	Unloaded		111	11											53					
3.5	Unloaded		114	22	7.9	0.14									49			43		
4.0	Unloaded		114	20	9.0	0.19									47			38		
4.5	Unloaded		108	20	9.6	0.22									49			36		
5.0	Unloaded		112	22	9.9	0.23									55			35		
5.5	Unloaded	181/106	114	21	10.5	0.24				7.29	28		587	67	50	59	9	36		0.50
6.0	10		113	21	12.8	0.35									50			31		
6.5	10		114	21	11.2	0.31									52			30		
7.0	20		113	21	12.6	0.36									55			30		
7.5	20	194/106	112	22	14.8	0.45				7.30	28		584	72	52	57	5	29		0.41
8.0	30		118	27	15.3	0.45									52			29		
8.5	30		119	23	18.1	0.57									53			28		
9.0	40		121	26	18.7	0.55									52			30		
9.5	40	200/106	123	24	19.9	0.65				7.29	28		580	74	54	59	5	27		0.42
10.0	50		127	24	20.8	0.68									54			28		
10.5	50		130	24	22.2	0.75									53			27		
11.0	60		132	25	22.8	0.76									54			27		
11.5	60	206/100	132	26	23.6	0.78				7.29	27		595	60	55	58	3	27		0.41
12.0	70		135	27	25.9	0.88									54			27		
12.5	70		138	29	25.8	0.91									57			26		
13.0	80		141	28	28.7	1.02									55			26		
13.5	80	213/106	144	29	29.8	1.07				7.27	28		601	50	57	62	5	26		0.42
14.0	90		149	26	30.0	1.14									57			24		
14.5	90		150	28	31.5	1.21									58			24		
15.0	100		153	30	33.8	1.28									58			24		
15.5	100	231/106	155	29	34.2	1.33				7.24	27		606	43	60	64	4	24		0.40
16.0	110		162	31	34.5	1.35									60			24		
16.5	110	234/119	159	39	35.4	1.40				7.23	26		583	66	62	64	2	23		0.37
17.0	120		165	34	37.3	1.52									64			23		
17.5	120		165	37	40.1	1.64									66			23		
18.0	Recovery		148	30	35.0	1.51									64			21		
18.5	Recovery		141	26	32.1	1.38									62			22		
19.0	Recovery		138	26	31.1	1.19									58			24		
19.5	Recovery	214/100	138	28	27.6	0.97				7.21	22		587	69	54	57	3	26		0.38

excluding a significant right-to-left shunt, and establishing that the exercise-associated hypoxemia on air breathing was due primarily to V:Q mismatch. Bicarbonate did not decrease in either study until 2 minutes after the exercise was terminated because of the increase in Pa_{CO_2} during exercise, which subsequently decreased in recovery.

Conclusion

Exercise performance was limited by severe obstructive lung disease. Oxygen breathing resulted in an increased work capacity despite the lack of hypoxemia at rest when breathing room air.

Case 50 Bullous Emphysema: Before and after Bullectomy

CLINICAL FINDINGS

This 50-year-old computer technician had retired approximately 10 years prior to initial evaluation because of progressive dyspnea. He was a heavy cigarette smoker. He denied cough, sputum production, wheezing, or chest pain. There was no family history of lung disease. Chest radiographs showed large bullae in the right middle and upper lung fields. Perfusion scan demonstrated no perfusion in these areas or at the left apex. α_1-Antitrypsin levels were normal. Exercise testing was performed to quantify his functional capacity in anticipation of surgical bullectomy. The patient subsequently underwent resection of the right upper lobe and affected portions of the right middle lobe. The resected lung showed bullous and centriacinar emphysema; a small squamous cell scar carcinoma was found in the upper lobe. Exercise testing was repeated 3 months after surgery.

EXERCISE FINDINGS

Preoperatively, the patient performed exercise on a cycle ergometer while breathing room air and, following a 90-minute rest, breathing 100% oxygen (not shown). At 3 months postoperatively, the air breathing study was repeated. On each occasion, he pedaled at 60 rpm on an unloaded cycle for 2 or 3 minutes. The work rate was then increased 20 W every minute. Arterial blood was sampled every second minute, and the intra-arterial blood pressure was recorded from a percutaneous brachial artery catheter. Resting ECGs were normal. On the preoperative studies, the patient stopped exercise because of dyspnea without an exercise-induced abnormality in the ECG. He stopped during the postoperative test because of dyspnea and pressure-like right-sided chest pain. There were multifocal, back-to-back, and salvos of premature ventricular contractions at the end of exercise and for 2 minutes of recovery without abnormal ST-segment changes.

Table 10.50.1

Selected Respiratory Function Data

Measurement	Predicted	Preoperative	Postoperative
Age (years)		50	
Sex		Male	
Height (cm)		170	
Weight (kg)	74	71	
Hematocrit (%)		46	
VC (L)	3.89	3.01	3.57
IC (L)	2.59	2.03	2.46
TLC (L)	5.69	7.05	5.56
FEV_1 (L)	3.09	1.93	2.44
FEV_1/VC (%)	79	64	68
MVV (L/min)	131	90	110
DLCO (mL/mm Hg/min)	26.5	10.0	13.0

INTERPRETATION

Comments

Resting respiratory function studies show moderate obstructive lung disease with marked reduction in DLCO. Flow rates did not improve following four breaths of nebulized isoproterenol. Following the bullectomy, the vital capacity increased, and the residual volume decreased with improvement in expiratory flow (Table 10.50.1). Although the diffusing capacity was slightly improved, it was still reduced disproportionately to the severity of airflow obstruction. For example, postoperatively, the MVV was 84% of predicted, whereas the DLCO was 50% of predicted. Despite the improvement in resting pulmonary function, exercise tolerance was only marginally improved postoperatively (Table 10.50.2 and Figs. 10.50.1 and 10.50.2).

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and anaerobic threshold were significantly reduced in both preoperative and postoperative tests (Table 10.50.2). See Flowchart 4 (Fig. 8.4). Preoperatively, the exercise breathing reserve is low, but postoperatively, the breathing reserve is normal (branch point 4.1). Following the "low breathing reserve" branch of the flowchart with respect to the preoperative study, VD/VT was high, consistent with lung disease with impaired peripheral oxygenation (branch point 4.2). Postbullectomy, the breathing reserve was normal, although the patient ended exercise at a similar level of ventilation. The ventilatory equivalent for CO_2 at the *AT* was lower than on the preoperative test but still higher than normal. Similarly, the indices of ventilation–perfusion mismatching derived from

arterial blood gas measurements ($P[A-a]O_2$, V_D/V_T, and $P[ET-a]O_2$) were less severely abnormal at peak exercise on the postoperative test, but were not normal. This indicates that pulmonary V:Q abnormalities persisted and were classified by the flowchart as "abnormal pulmonary circulation" (at branch point 4.5) with low SaO_2 and normal vital capacity, further suggesting "pulmonary vascular disease" as the underlying pathophysiology. This is consistent with the patient's low resting DLCO. A right-to-left shunt was excluded as the cause of hypoxemia by the exercise test performed while breathing 100% oxygen (not shown). Other findings characteristic of abnormalities of the pulmonary circulation include: (1) a steep heart rate response to the increase in $\dot{V}O_2$, becoming steeper as the peak $\dot{V}O_2$ was approached (panel 3); (2) a low O_2 pulse with a flat contour as the work rate was increased (panel 2); and (3) a decreasing $\Delta\dot{V}O_2/\Delta WR$ as the work rate was increased (panel 1). These findings were prominent in both the preoperative test (Fig. 10.50.1) and the postoperative test (Fig. 10.50.2) and suggest functionally important pulmonary vascular disease. Although the bullectomy improved ventilatory mechanics, it did not significantly improve the abnormalities in peak $\dot{V}O_2$.

Conclusion

The patient had mild-to-moderate obstructive lung disease with hyperinflation due to bullous lung disease. Lung mechanics improved following resectional surgery of the bullae. Postoperatively, he was no longer ventilatory limited, had less wasted ventilation, and less severe hypoxemia during exercise. However, maximal exercise capacity improved very little due to persistent pulmonary vascular impairment as evidenced by a very high $\dot{V}E/\dot{V}CO_2$ *@ AT* (around 64) and V_D/V_T (around 0.40) (Tables 10.50.3 and 10.50.4).

Table 10.50.2

Selected Exercise Data

Measurement	Predicted	Preoperative	Postoperative
Peak $\dot{V}O_2$ (L/min)	2.32	0.99	1.06
Maximum heart rate (beats/min)	170	144	144
Maximum O_2 pulse (mL/beat)	13.7	7.5	7.9
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	5.1	5.8
AT (L/min)	>1.00	0.6	0.75
Blood pressure (mm Hg [rest, max])		144/90, 187/100	144/88, 238/94
Maximum $\dot{V}E$ (L/min)		84	80
Exercise breathing reserve (L/min)	>15	6	30
$\dot{V}E/\dot{V}CO_2$ *@ AT* or lowest	27.1	56.0	44.5
PaO_2 (mm Hg [rest, max ex])		67, 54	74, 74
$P(A-a)O_2$ (mm Hg [rest, max ex])		47, 72	34, 52
$PaCO_2$ (mm Hg [rest, max ex])		30, 28	34, 31
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		4, 8	4, 3
V_D/V_T (rest, heavy ex)		0.39, 0.47	0.41, 0.40
HCO_3^- (mEq/L [rest, 2-min recov])		21, 14	21, 14

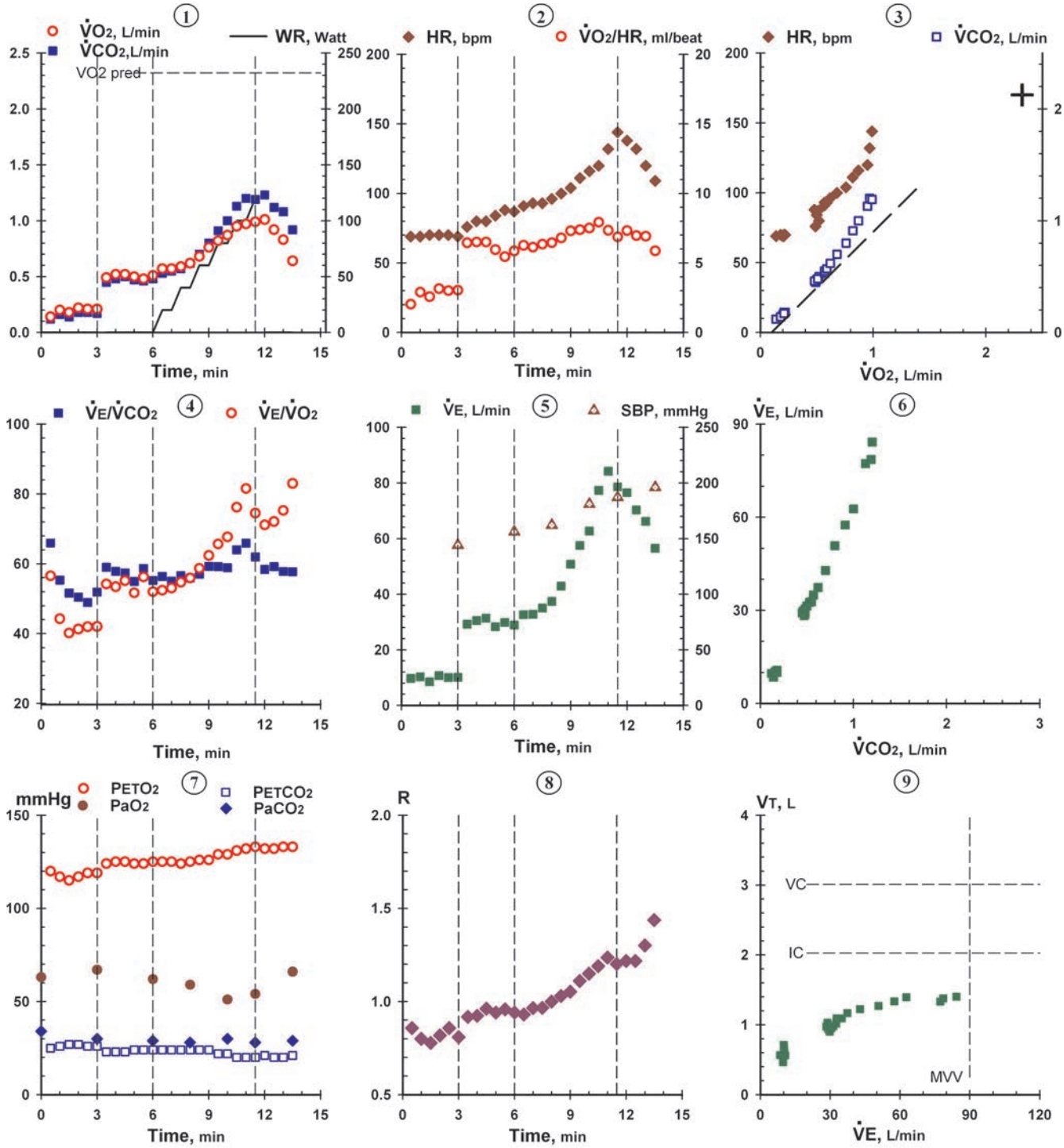

FIGURE 10.50.1. Preoperative. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

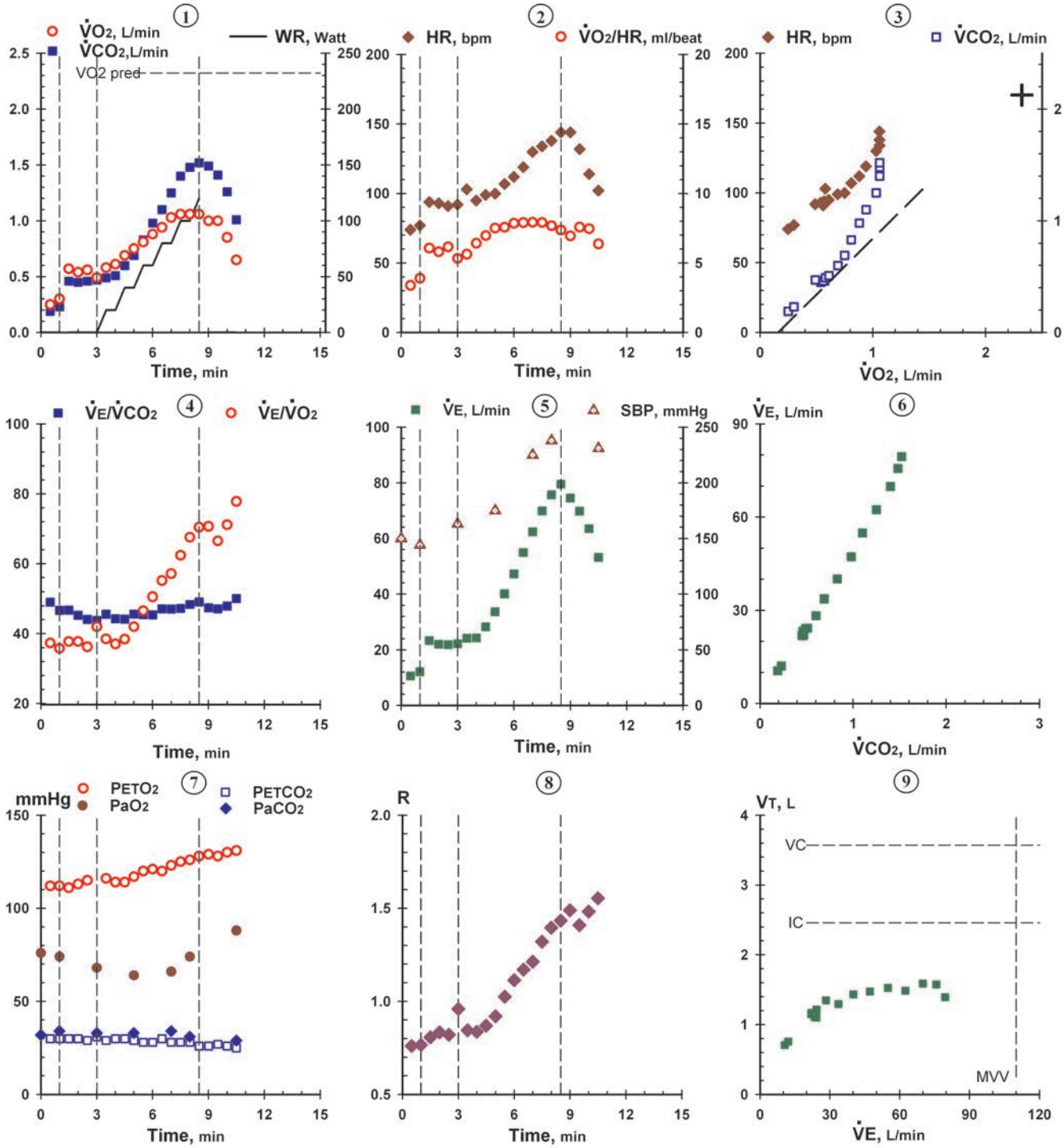

FIGURE 10.50.2. Postoperative. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.50.3

Prebullectomy Study

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest									7.41	21		63			34				
0.5	Rest		69	21	9.7	0.12	0.14	2.0	0.86			120			25			66	57	
1.0	Rest		69	17	10.3	0.16	0.20	2.9	0.80			117			26			55	44	
1.5	Rest		70	15	8.5	0.14	0.18	2.6	0.78			115			27			52	40	
2.0	Rest		70	19	10.7	0.18	0.22	3.1	0.82			117			27			50	41	
2.5	Rest		70	14	10.0	0.18	0.21	3.0	0.86			119			26			49	42	
3.0	Rest	144/90	69	15	10.1	0.17	0.21	3.0	0.81	7.41	19	119	67	47	26	30	4	52	42	0.39
3.5	Unloaded		76	31	29.2	0.45	0.49	6.4	0.92			124			23			59	54	
4.0	Unloaded		80	32	30.5	0.48	0.52	6.5	0.92			125			23			58	53	
4.5	Unloaded		80	32	31.4	0.50	0.52	6.5	0.96			125			23			57	55	
5.0	Unloaded		84	29	28.3	0.47	0.50	6.0	0.94			124			24			55	52	
5.5	Unloaded		88	33	29.8	0.46	0.48	5.5	0.96			124			24			59	56	
6.0	Unloaded	156/90	87	28	28.9	0.48	0.51	5.9	0.94	7.41	18	125	62	58	24	29	5	55	52	0.42
6.5	20		91	32	32.6	0.53	0.57	6.3	0.93			125			24			56	52	
7.0	20		93	30	32.8	0.55	0.57	6.1	0.96			125			24			55	53	
7.5	40		93	32	35.0	0.57	0.59	6.3	0.97			124			24			57	55	
8.0	40	162/94	96	32	37.4	0.62	0.62	6.5	1.00	7.40	17	125	59	63	24	28	4	56	56	0.42
8.5	60		100	35	42.9	0.70	0.68	6.8	1.03			126			24			57	59	
9.0	60		104	40	50.8	0.80	0.76	7.3	1.05			126			24			59	62	
9.5	80		111	43	57.5	0.91	0.82	7.4	1.11			129			22			59	66	
10.0	80	181/96	116	45	62.7	1.00	0.87	7.5	1.15	7.40	18	129	51	72	22	30	8	59	68	0.48
10.5	100		120	58	77.3	1.13	0.95	7.9	1.19			131			20			64	76	
11.0	100		132	60	84.2	1.20	0.97	7.3	1.24			132			20			66	82	
11.5	120	187/100	144	57	78.6	1.19	0.99	6.9	1.20	7.39	17	133	54	72	20	28	8	62	75	0.47
12.0	Recovery		138	55	76.5	1.23	1.01	7.3	1.22			132			21			58	71	
12.5	Recovery		132	47	70.3	1.12	0.92	7.0	1.22			132			20			59	72	
13.0	Recovery		120	44	66.2	1.08	0.83	6.9	1.30			133			20			58	75	
13.5	Recovery	196/99	109	40	56.5	0.92	0.64	5.9	1.44	7.31	14	133	66	62	21	29	8	58	83	0.46

Table 10.50.4

Postbullectomy Study

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	150/94								7.44	21		76			32				
0.5	Rest		74	15	10.6	0.19	0.25	3.4	0.76			112			30			49	37	
1.0	Rest	144/88	77	16	12.1	0.23	0.30	3.9	0.77	7.42	22	112	74	34	30	34		47	36	0.41
1.5	Unloaded		94	21	23.3	0.46	0.57	6.1	0.81			111			30			47	38	
2.0	Unloaded		93	19	22.0	0.45	0.54	5.8	0.83			113			30			45	38	
2.5	Unloaded		91	19	21.9	0.46	0.56	6.2	0.82			115			29			44	36	
3.0	Unloaded	163/38	92	19	22.2	0.47	0.49	5.3	0.96	7.42	21	115	68	48	31	33	2	44	42	0.37
3.5	20		103	22	24.2	0.49	0.58	5.6	0.84			116			29			46	39	
4.0	20		95	20	24.3	0.51	0.61	6.4	0.84			114			30			44	37	
4.5	40		99	21	28.3	0.60	0.69	7.0	0.87			114			30			44	38	
5.0	40	175/94	100	26	33.7	0.69	0.75	7.5	0.92	7.42	21	117	64	51	29	33	4	46	42	0.40
5.5	60		107	28	40.1	0.83	0.81	7.6	1.02			120			28			45	47	
6.0	60		112	32	47.2	0.98	0.88	7.9	1.11			121			28			45	51	
6.5	80		119	36	54.9	1.10	0.94	7.9	1.17			120			30			47	55	
7.0	80	225/94	130	42	62.4	1.25	1.03	7.9	1.21	7.39	20	123	66	55	28	34	6	47	57	0.43
7.5	100		134	44	69.9	1.40	1.06	7.9	1.32			125			28			47	62	
8.0	100	238/94	138	48	75.7	1.48	1.06	7.7	1.40	7.35	17	126	74	52	28	31	3	48	68	0.40
8.5	120		144	57	79.5	1.52	1.06	7.4	1.43			128			26			49	70	
9.0	Recovery		144	45	74.5	1.49	1.00	6.9	1.49			129			26			47	71	
9.5	Recovery		132	39	69.8	1.41	1.00	7.6	1.41			128			27			47	66	
10.0	Recovery		114	36	63.5	1.26	0.85	7.5	1.48			130			26			48	71	
10.5	Recovery	231/100	102	31	53.2	1.01	0.65	6.4	1.55	7.31	14	131	88	41	25	29	4	50	78	0.39

Case 51 Chronic Obstructive Lung Disease with a History of Heart Failure

CLINICAL FINDINGS

This 50-year-old meat cutter and former smoker had severe exertional dyspnea and had been hospitalized on several occasions for what was considered congestive heart failure, characterized by wheezing, leg edema, and orthopnea. He was referred for exercise testing to aid in distinguishing between cardiac and respiratory disease. He had an anemia of unknown cause (Table 10.51.1). Breath sounds were distant on exam.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 2 minutes. The work rate was then increased 15 W per minute to tolerance. Arterial blood was sampled every second minute, and intra-arterial pressure was recorded from a percutaneously placed brachial artery catheter. Heart rate and rhythm were continuously monitored; 12-lead ECGs were obtained during rest, exercise, and recovery. The patient appeared to give an excellent effort and stopped exercise because of severe dyspnea and exhaustion. He denied chest pain. No arrhythmias or ischemic changes were noted on the ECGs.

Table 10.51.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		50
Sex		Male
Height (cm)		174
Weight (kg)	77	91
Hemoglobin (g/100 mL)		10.3
VC (L)	4.40	3.11
IC (L)	2.94	2.15
TLC (L)	6.44	9.78
FEV_1 (L)	3.49	1.14
FEV_1/VC (%)	79	37
MVV (L/min)	147	45
D_{LCO} (mL/mm Hg/min)	24.4	28.8

INTERPRETATION

Comments

Resting respiratory function studies showed severe obstructive lung disease with hyperinflation and no improvement in flow rates following inhaled albuterol but

Table 10.51.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.55	1.20
Maximum heart rate (beats/min)	170	147
Maximum O_2 pulse (mL/beat)	14.3	8.4
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	7.6
AT (L/min)	>1.10	0.95
Blood pressure (mm Hg [rest, max])		135/90, 180/84
Maximum $\dot{V}_E$ (L/min)		41
Exercise breathing reserve (L/min)	>15	4
$\dot{V}_E/\dot{V}CO_2$ @ *AT* or lowest	27.0	29.1
PaO_2 (mm Hg [rest, max ex])		84, 76
$P(A-a)O_2$ (mm Hg [rest, max ex])		19, 21
$PaCO_2$ (mm Hg [rest, max ex])		43, 58
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		5, 5
V_D/V_T (rest, heavy ex)		0.43, 0.46
HCO_3^- (mEq/L [rest, 2-min recov])		31, 29

with an above-predicted DLCO (see Table 10.51.1). The predicted value for DLCO was adjusted for the patient's anemia. Arterial blood gases at rest showed chronic compensated respiratory acidosis with normal oxygenation. The patient was also overweight.

Analysis

The peak $\dot{V}O_2$ and anaerobic threshold were both decreased (Table 10.51.2). In Figure 10.51.1, the striking finding is obvious ventilatory limitation (panel 9) as ventilation approached the patient's MVV, accompanied by increasing $PaCO_2$ over the course of the test (Table 10.51.3). Because ventilation did not keep pace with CO_2 production, the $\dot{V}E/\dot{V}CO_2$ ratio at the *AT* (panel 4) and the slope of $\dot{V}E$ as a function of VCO_2 (panel 6) appear normal. The VD/VT is elevated, however, as calculated from the arterial blood gas data (see Tables 10.51.2 and 10.51.3). Arterial oxygenation and $P(A - a)O_2$ were relatively normal, indicating that the major gas exchange abnormalities were related to high V:Q regions without significant low V:Q regions. Despite this, there are abnormalities in effective O_2 flow as reflected in the low *AT* and steepening of heart rate relative to $\dot{V}O_2$ in mid exercise (see Fig. 10.51.1, panel 3). These findings can be attributed, at least in part, to the reduced oxygen carrying capacity due to anemia. Additional cardiovascular factors in the form of secondary pulmonary vascular disease or comorbid left ventricular disease may also contribute.

If this case were classified using the flowcharts, there could reasonably be a number of different conclusions. Following branch points 1.1, 1.2, and 1.3 of Flowchart 1 (Fig. 8.1) leads to Flowchart 4 (Fig. 8.4). The low breathing reserve (branch point 4.1) and the high VD/VT (branch point 4.2) lead to the diagnosis labeled "lung disease with impaired peripheral oxygenation." However, the patient's data do not perfectly fit the conditions listed under this category. He does, however, have a low arterial O_2 content and many of the other factors listed in the "pulmonary vascular disease" category. Following Flowchart 5 (Fig. 8.5), instead, through branch points 5.1, 5.3, and 5.7, would lead to the category of "obstructive lung disease," which the patient clearly has. However, it may not fully account for the low $\Delta\dot{V}O_2/\Delta WR$ and flat O_2 pulse, which indicate a problem with O_2 flow.

Conclusion

The presence of comorbid and/or secondary disease in this patient with obstructive lung disease results in multiple abnormalities of the exercise response in addition to ventilatory limitation.

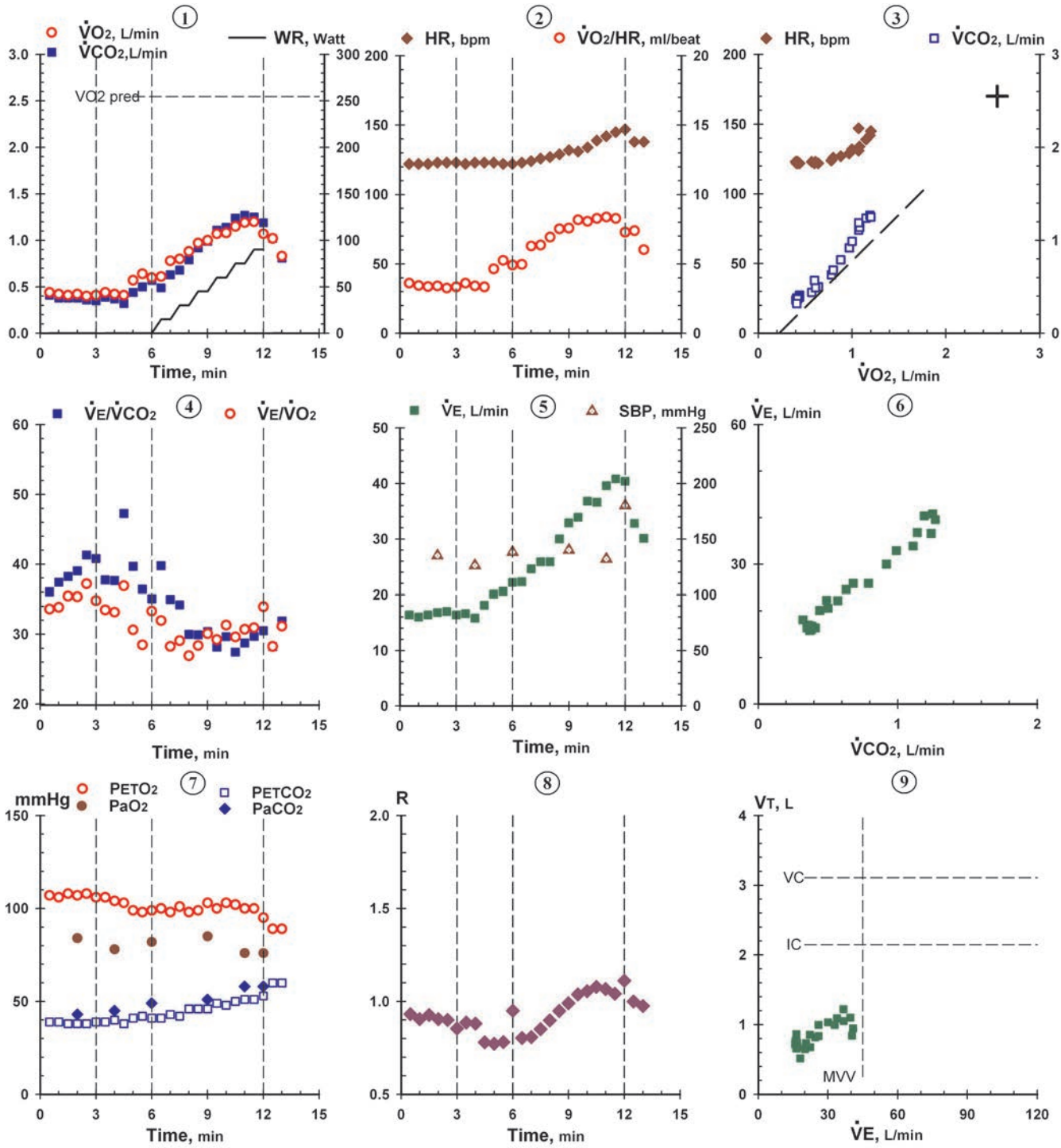

FIGURE 10.51.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.51.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	*a*	$(A-a)$	*ET*	*a*	$(a-ET)$			
0	Rest		122	19	16.4	0.41	0.44	3.6	0.93			107			39			36	34	
0.5	Rest		122	21	16.0	0.38	0.42	3.4	0.90			106			39			37	34	
1.0	Rest		122	22	16.4	0.38	0.41	3.4	0.93			108			38			38	35	
1.5	Rest	135/90	123	23	16.8	0.38	0.42	3.4	0.90	7.48	31	107	84	19	38	43	5	39	35	0.43
2.0	Rest		123	25	17.0	0.36	0.40	3.3	0.90			108			38			41	37	
2.5	Rest		123	25	16.4	0.35	0.41	3.3	0.85			106			39			41	35	
3.0	Rest		122	22	16.6	0.39	0.44	3.6	0.89			106			39			38	33	
3.5	Rest	126/84	123	22	15.8	0.37	0.42	3.4	0.88	7.46	31	104	78	22	40	45	5	38	33	0.43
4.0	Unloaded		123	35	18.1	0.32	0.41	3.3	0.78			103			38			47	37	
4.5	Unloaded		123	31	20.1	0.44	0.57	4.6	0.77			99			41			40	31	
5.0	Unloaded		122	28	20.6	0.50	0.64	5.2	0.78			98			42			36	28	
5.5	Unloaded	138/90	122	26	22.2	0.57	0.60	4.9	0.95	7.42	31	99	82	17	41	49	8	35	33	0.45
6.0	15		123	33	22.3	0.49	0.61	5.0	0.80			100			41			40	32	
6.5	15		124	30	24.6	0.63	0.78	6.3	0.81			98			43			35	28	
7.0	30		126	31	25.9	0.68	0.80	6.3	0.85			101			42			34	29	
7.5	30		127	26	25.9	0.79	0.88	6.9	0.90			98			46			30	27	
8.0	45		129	29	30.0	0.92	0.97	7.5	0.95			99			46			30	28	
8.5	45	140/78	132	33	32.9	0.99	1.00	7.6	0.99	7.38	30	103	85	14	46	51	5	30	30	0.41
9.0	60		131	31	33.9	1.11	1.07	8.2	1.04			100			49			28	29	
9.5	60		134	35	36.8	1.14	1.08	8.1	1.06			103			48			30	31	
10.0	75		139	30	36.6	1.24	1.15	8.3	1.08			102			50			27	30	
10.5	75	132/84	142	36	39.6	1.27	1.19	8.4	1.07	7.32	29	100	76	19	51	58	7	29	31	0.45
11.0	90		145	43	40.8	1.25	1.20	8.3	1.04			100			51			30	31	
11.5	90	180/84	147	48	40.4	1.19	1.07	7.3	1.11	7.32	29	95	76	21	53	58	5	31	34	0.46
12.0	Recovery		138	47	32.8	1.02	1.02	7.4	1.00			89			60			28	28	
12.5	Recovery		138	50	30.1	0.81	0.83	6.0	0.98			89			60			32	31	

Case 52 Mild Obstructive Airway Disease with Disproportionate Exertional Dyspnea

CLINICAL FINDINGS

This 64-year-old retired shipyard worker was evaluated because of increasing shortness of breath that had begun 7 years previously and had progressed to become evident with walking two blocks or climbing a flight of stairs. He had smoked half a pack of cigarettes daily from age 40 to 60. He had also been treated for pulmonary tuberculosis 2 decades previously. Prostatic carcinoma had been found 8 months previously at the time of transurethral prostatectomy. He was treated with triamterene, hydrochlorothiazide, and methyldopa for systemic hypertension. The chest radiographs revealed a single small pleural plaque on the left, evidence of old granulomatous disease in the right apex, and flat diaphragms. Airflow obstruction was evident on pulmonary function tests. Exercise testing was requested, however, because the patient's symptoms seemed disproportionate to the degree of pulmonary function abnormality.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 15 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. A resting ECG showed some premature atrial and ventricular contractions, poor R-wave progression from leads V_1 through V_3, and left atrial enlargement. At 90 W, there were occasional pairs of premature ventricular contractions and two episodes of ventricular bigeminy. The patient stopped exercising because of shortness of breath. Under questioning, he also conceded that he had felt some substernal tightness at the highest work rate.

INTERPRETATION

Comments

The results of the resting respiratory function studies showed hyperinflation and expiratory airflow obstruction. The FEV_1 was within the normal range, but FEV_1/VC was mildly to moderately reduced (60%), and there was a moderately severe reduction of DLCO (Table 10.52.1). The resting ECG showed premature atrial and ventricular contractions and poor R-wave progression from V_1 to V_3. The arterial

Table 10.52.1

Selected Respiratory Function Data

Measurement	Predicted	Measured	
Age (years)		64	
Sex		Male	
Height (cm)		178	
Weight (kg)	80	82	
Hematocrit (%)		47	
		Before bronchodilator	After bronchodilator
VC (L)	3.82	4.52	4.75
IC (L)	2.55	3.25	
TLC (L)	5.93	8.66	
FEV_1 (L)	2.98	2.69	2.78
FEV_1/VC (%)	78	60	58
MVV (L/min)	121	90	112
DLCO (mL/mm Hg/min)	24.8	14.0	

blood pressure was also elevated, even taking into consideration that the directly recorded pressures may exceed cuff pressures by 10 mm Hg. Given this degree of resting hypertension, testing might have been deferred pending better control of blood pressure. In this case, exercise testing proceeded with caution.

Analysis

The peak $\dot{V}O_2$ was considerably reduced relative to predicted (Table 10.52.2). The anaerobic threshold was difficult to determine with certainty (Fig. 10.52.1, panel 3). The test ended as the patient's ventilation reached his MVV, indicating that he had reached his ventilatory capacity. This is despite relatively modest airflow obstruction on resting pulmonary function tests. The explanation for this is found in the high ventilatory equivalents. These were elevated to a minor degree by hyperventilation ($PaCO_2$ values 32 to 34 mm Hg) but for the most part reflect higher than normal VD/VT (Tables 10.52.2 and 10.52.3). The primary finding of this test, therefore, was that the patient had a greater exercise impairment than would be predicted by his FEV_1. This might be due entirely to mismatching of ventilation to perfusion, resulting in the very elevated VD/VT and low DLCO. However, the exercise-associated hypoxemia and the directional changes in ventilatory equivalents with exercise (see Fig. 10.52.1, panel 4) could reflect a development of right-to-left shunting through a patent foramen ovale, which sometimes occurs in patients with obstructive lung disease if there is sufficient pulmonary vascular disease to elevate right atrial pressures. Measurement of exercise blood gases while breathing 100% oxygen would have clarified whether this occurred. Alternatively, the patient's rapid breathing frequency during exercise may have led to dynamic hyperinflation, consistent with the relatively low VT/IC ratio throughout exercise (see Fig. 10.52.1, panel 9), which would tend to increase VD/VT. No measurements of inspiratory capacity were made during exercise to identify whether there was a change in end-expiratory lung volume to support this.

As in many other cases of lung disease presented in this chapter, the test also included findings reflecting impaired O_2 flow, including a low $\dot{V}O_2$/WR (see Fig. 10.52.1, panel 1) and steep increase in heart rate relative to $\dot{V}O_2$ (see Fig. 10.52.1 panel 3). These are consistent with the effect of hyperinflation on cardiac function or coexistent cardiac or pulmonary vascular pathophysiology. Although the patient experienced chest pressure at peak exercise, there were no ECG findings to indicate myocardial ischemia, nor was there a distinct change in the relationship of heart rate to $\dot{V}O_2$ at the time of symptoms.

Table 10.52.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.16	1.42
Maximum heart rate (beats/min)	156	159
Maximum O_2 pulse (mL/beat)	13.9	8.9
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.3	8.1
AT (L/min)	>0.95	Indeterminate
Blood pressure (mm Hg [rest, max])		186/116, 263/128
Maximum $\dot{V}E$ (L/min)		91
Exercise breathing reserve (L/min)	>15	91
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.3	42.4
PaO_2 (mm Hg [rest, max ex])		79, 57
$P(A-a)O_2$ (mm Hg [rest, max ex])		38, 65
$PaCO_2$ (mm Hg [rest, max ex])		32, 31
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		4, 9
VD/VT (rest, heavy ex)		0.38, 0.47
HCO_3^- (mEq/L [rest, 2-min recov])		24, 17

Conclusion

This case is presented to illustrate the considerable amount of gas exchange abnormality that can occur during exercise, even with only mild abnormalities in spirometry.

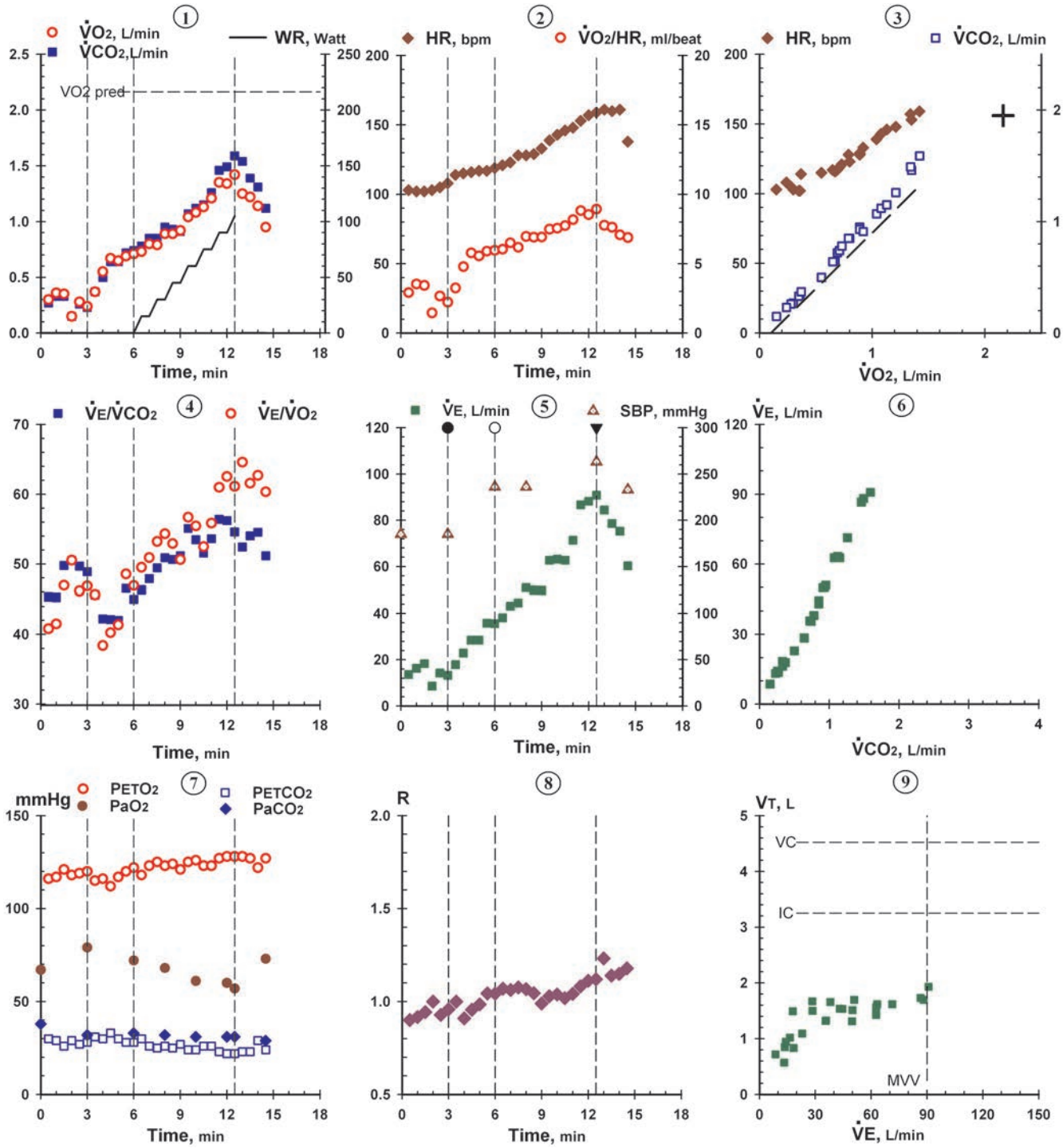

FIGURE 10.52.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.52.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	185/116								7.42	24		67			38				
0.5	Rest		103	16	13.6	0.27	0.30	2.9	0.90			116			30			45	41	
1.0	Rest		102	16	16.3	0.33	0.36	3.5	0.92			117			29			45	42	
1.5	Rest		102	22	18.3	0.33	0.35	3.4	0.94			121			26			50	47	
2.0	Rest		103	12	8.6	0.15	0.15	1.5	1.00			118			29			51	51	
2.5	Rest		105	15	14.2	0.26	0.28	2.7	0.93			119			27			50	46	
3.0	Rest	185/116	108	23	13.2	0.23	0.24	2.2	0.96	7.46	22	120	79	38	28	32	4	49	47	0.38
3.5	Unloaded		114	12	17.9	0.37	0.37	3.2	1.00			115			31			46	46	
4.0	Unloaded		115	21	22.9	0.50	0.55	4.8	0.91			116			30			42	38	
4.5	Unloaded		116	17	28.4	0.64	0.67	5.8	0.96			112			33			42	40	
5.0	Unloaded		117	19	28.5	0.64	0.65	5.6	0.98			117			30			42	41	
5.5	Unloaded		117	27	35.8	0.72	0.69	5.9	1.04			120			28			47	49	
6.0	Unloaded	236/126	119	27	35.6	0.74	0.71	6.0	1.04	7.43	22	122	72	46	28	33	5	45	47	0.39
6.5	15		121	23	38.1	0.78	0.73	6.0	1.07			118			30			46	50	
7.0	15		123	28	43.1	0.85	0.80	6.5	1.06			123			26			48	51	
7.5	30		128	29	44.5	0.85	0.79	6.2	1.08			125			25			49	53	
8.0	30	236/128	128	30	50.9	0.95	0.89	7.0	1.07	7.44	21	123	68	52	26	32	6	51	54	0.45
8.5	45		129	33	49.9	0.93	0.89	6.9	1.04			124			25			51	53	
9.0	45		133	38	49.8	0.91	0.92	6.9	0.99			121			27			51	51	
9.5	60		139	44	62.7	1.07	1.04	7.5	1.03			125			24			55	57	
10.0	60		143	39	63.2	1.12	1.08	7.6	1.04	7.44	21	126	61	59	24	31	7	53	55	0.45
10.5	75		146	40	62.7	1.15	1.13	7.7	1.02			123			26			52	52	
11.0	75		148	44	71.3	1.26	1.21	8.2	1.04			123			26			54	56	
11.5	90		153	50	86.6	1.46	1.35	8.8	1.08			127			23			56	61	
12.0	90		157	52	88.2	1.49	1.34	8.5	1.11	7.42	20	128	60	61	22	31	9	56	63	0.48
12.5	105	263/128	159	47	90.8	1.59	1.42	8.9	1.12	7.41	19	128	57	65	22	31	9	55	61	0.47
13.0	Recovery		161	43	84.4	1.54	1.25	7.8	1.23			128			23			52	65	
13.5	Recovery		160	41	78.6	1.39	1.22	7.6	1.14			127			23			54	62	
14.0	Recovery		161	44	75.2	1.31	1.14	7.1	1.15			122			29			55	63	
14.5	Recovery	233/139	138	35	60.3	1.12	0.95	6.9	1.18	7.39	17	127	73	51	24	29	5	51	60	0.40

Case 53 Mild Pulmonary Asbestosis

CLINICAL FINDINGS

This 55-year-old male shipyard worker had a long history of asbestos exposure and was a former cigarette smoker. He had a daily cough productive of scant, yellow-tinged sputum but noted shortness of breath only after climbing three to four flights of stairs. He denied any other symptoms or illnesses. No rales were noted on examination. Chest radiograph revealed minimal, but definite, basilar fibrosis, which is typical of asbestosis. Exercise testing was requested to identify the presence and degree of physiologic impairment associated with the asbestosis.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 10 W per minute to tolerance. Arterial blood was sampled every second minute, and intra-arterial pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of shortness of breath. The ECG showed nonspecific T-wave abnormalities and occasional premature ventricular contractions at rest and during exercise.

Table 10.53.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		55
Sex		Male
Height (cm)		181
Weight (kg)	82	84
Hematocrit (%)		45
VC (L)	4.24	3.50
IC (L)	2.83	2.26
TLC (L)	6.32	5.15
FEV_1 (L)	3.35	2.94
FEV_1/VC (%)	79	84
MVV (L/min)	135	107
D_{LCO} (mL/mm Hg/min)	27.3	22.7

INTERPRETATION

Comments

Resting pulmonary function studies showed a mild restrictive defect with proportionate reduction in D_{LCO}, suggesting loss of pulmonary capillary bed (Table 10.53.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ was decreased but the anaerobic threshold was normal (Table 10.53.2). Referring to Flowchart 3 (Fig. 8.3), at branch point 3.1, the breathing reserve was borderline low. The flowchart prompts us to review the gas exchange abnormalities

Table 10.53.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.50	2.03
Maximum heart rate (beats/min)	165	154
Maximum O_2 pulse (mL/beat)	15.1	13.2
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.7
AT (L/min)	>1.08	1.3
Blood pressure (mm Hg [rest, max])		156/90, 216/99
Maximum $\dot{V}_E$ (L/min)		93
Exercise breathing reserve (L/min)	>15	14
$\dot{V}_E/\dot{V}CO_2$ @ *AT* or lowest	27.2	31.0
PaO_2 (mm Hg [rest, max ex])		88, 99
$P(A-a)O_2$ (mm Hg [rest, max ex])		14, 21
$PaCO_2$ (mm Hg [rest, max ex])		38, 32
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		3, –2
V_D/V_T (rest, max ex)		0.37, 0.30
HCO_3^- (mEq/L [rest, 2-min recov])		25, 20

Table 10.53.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	156/90								7.43	25		79			38				
0.5	Rest		81	21	12.3	0.24	0.32	4.0	0.75			106			35			44	33	
1.0	Rest		83	23	11.8	0.23	0.31	3.7	0.74			106			35			43	32	
1.5	Rest		88	21	11.9	0.23	0.30	3.4	0.77			108			34			44	34	
2.0	Rest	162/96	80	22	11.2	0.23	0.31	3.9	0.74	7.42	24	105	88	14	35	38	3	41	30	0.37
2.5	Rest		84	18	11.4	0.23	0.31	3.7	0.74			104			36			43	32	
3.0	Rest		86	20	12.2	0.25	0.32	3.7	0.78			106			36			42	33	
3.5	Unloaded		97	21	16.3	0.40	0.50	5.2	0.80			105			37			36	29	
4.0	Unloaded		93	33	21.8	0.48	0.66	7.1	0.73			102			37			40	29	
4.5	Unloaded		93	32	23.8	0.52	0.64	6.9	0.81			109			34			41	33	
5.0	Unloaded		95	30	22.7	0.53	0.69	7.3	0.77			104			37			38	29	
5.5	Unloaded		94	36	22.3	0.51	0.67	7.1	0.76			100			38			38	29	
6.0	Unloaded	192/96	96	35	29.2	0.65	0.75	7.8	0.87	7.43	25	108	91	16	34	38	4	40	35	0.39
6.5	20		97	36	26.6	0.62	0.78	8.0	0.79			105			36			38	30	
7.0	20		98	39	28.3	0.62	0.78	8.0	0.79			108			35	38		40	32	
7.5	40		95	41	28.7	0.62	0.80	8.4	0.78			204			37			41	32	
8.0	40	192/90	103	26	27.7	0.75	0.98	9.5	0.77	7.43	25	101	87	16	38		0	34	26	0.31
8.5	60		104	31	28.3	0.73	0.91	8.8	0.80			104			37			35	28	
9.0	60		110	35	40.2	1.02	1.16	10.5	0.88			110			35	40		36	32	
9.5	80		113	36	39.6	1.06	1.29	11.4	0.82			104			38			34	28	
10.0	80	198/93	120	28	35.4	1.07	1.41	11.8	0.76	7.41	25	97	89	11	42		–2	31	23	0.28
10.5	100		128	37	47.4	1.26	1.39	10.9	0.91			110			37			35	32	
11.0	100		130	52	55.2	1.36	1.44	11.1	0.94			113			35	35		37	35	
11.5	120		130	49	60.6	1.50	1.50	11.5	1.00			113			35			38	38	
12.0	120	201/93	131	58	66.8	1.64	1.67	12.7	0.98	7.43	23	114	98	16	34		1	38	37	0.32
12.5	140		138	50	68.0	1.73	1.72	12.5	1.01			114			35			37	37	
13.0	140		140	50	73.4	1.87	1.78	12.7	1.05			115			35	33		37	39	
13.5	160		148	60	87.0	2.09	1.93	13.0	1.08			119			32	32		39	42	
14.0	160	198/99	149	59	92.9	2.24	2.03	13.6	1.10	7.43	22	119	99	20	32		1	39	43	0.32
14.5	180	216/99	154	55	89.3	2.21	2.02	13.1	1.09	7.42	20	117	99	21	34		–2	38	42	0.28
15.0	Recovery		146	32	61.5	1.73	1.64	11.2	1.05			115			35			34	36	
15.5	Recovery		132	32	53.4	1.37	1.14	8.6	1.20			118			35	33		37	44	
16.0	Recovery		128	28	37.8	0.96	0.76	5.9	1.26			121			33			37	47	
16.5	Recovery	189/93	125	27	30.1	0.75	0.63	5.0	1.19	7.39	20	119	114	7	34		–1	37	44	0.27

usually associated with lung diseases. These were borderline, with VD/VT around the upper limit of normal at rest, and at or above the upper limit of normal at peak exercise as reflected in the last two exercise values, which averaged 0.30 (Table 10.53.3). Similarly, the overall relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ appears abnormal (Fig. 10.53.1, panels 4 and 6), even though the value measured at the *AT* is only a little higher than the upper limit of the normal range (see Table 10.53.2). The $P(A - a)O_2$ and $P(a - ET)CO_2$ values were within normal ranges. These findings indicate mildly abnormal V:Q matching associated with the patient's interstitial lung disease. At branch point 3.2, the high breathing frequency is characteristic of restrictive lung disease.

Conclusion

This patient with pulmonary asbestosis had mild restrictive lung disease at rest. Exercise testing revealed lower than normal peak $\dot{V}_{O_2}$. The high breathing frequency and low breathing reserve in response to maximal exercise testing support the conclusion that exercise was limited by ventilatory restriction. Measurements of ventilation–perfusion matching were also abnormal.

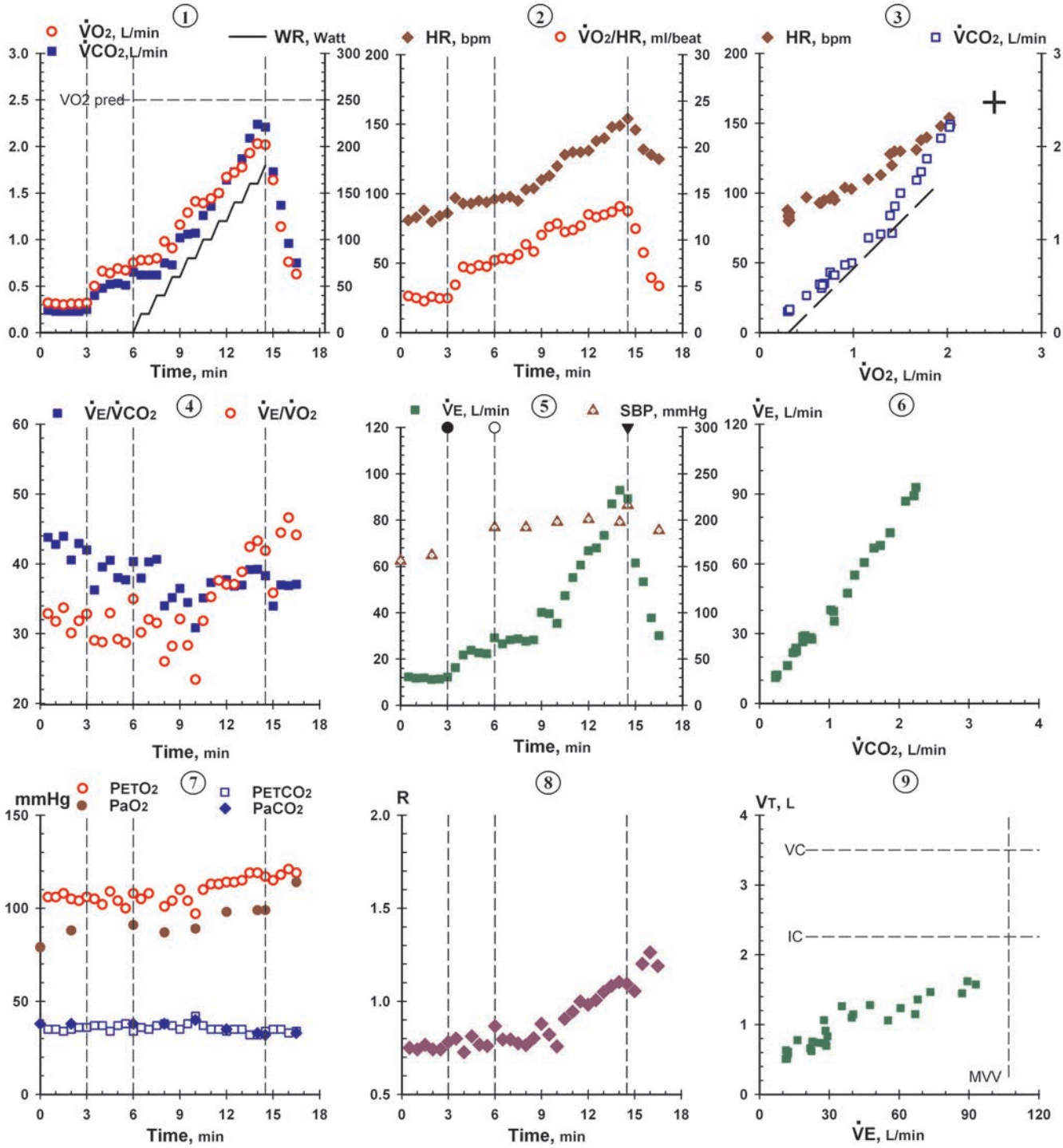

FIGURE 10.53.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 54 Severe Pulmonary Asbestosis

CLINICAL FINDINGS

This 67-year-old woman was referred for exercise testing for assessment of her functional capacity. She had been exposed to asbestos for 3 years while working in a shipyard approximately 40 years earlier. She had never smoked. Three years prior to this evaluation, she noted fatigability, clubbing of fingernails, and shortness of breath. She was unable to climb a flight of stairs or walk rapidly on level ground. A transbronchial lung biopsy was reported to show "fibrosis." Her symptoms improved significantly on treatment with prednisone, but this was discontinued after 1 year because of concern for side effects. Five months prior to this evaluation, she was started on oxygen therapy, but corticosteroids were not restarted. Examination revealed a thin woman with fine inspiratory rales in the lateral and inferior lung fields that did not clear with coughing. There was dramatic digital clubbing. Chest radiographs showed extensive interstitial infiltrates, compatible with pulmonary fibrosis. There was also a small patch of pleural calcification consistent with asbestos-related pleural disease. A resting ECG was normal.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. She pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 10 W per minute to her symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercising because of dyspnea. Premature atrial contractions occurred during exercise, but the ECG otherwise was not remarkable.

Table 10.54.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		67
Sex		Female
Height (cm)		163
Weight (kg)	63	48
Hematocrit (%)		38
VC (L)	2.77	1.51
IC (L)	1.85	0.70
TLC (L)	4.82	2.65
FEV_1 (L)	2.19	1.24
FEV_1/VC (%)	79	82
MVV (L/min)	82	33
DLCO (mL/mm Hg/min)	22.3	6.4

INTERPRETATION

Comments

Results of the respiratory function studies indicate a severe restrictive defect with a marked reduction in diffusing capacity (Table 10.54.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ was reduced at less than half the predicted value, and the anaerobic threshold was indeterminate (Table 10.54.2).

Table 10.54.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.12	0.42
Maximum heart rate (beats/min)	153	108
Maximum O_2 pulse (mL/beat)	7.3	4.1
AT (L/min)	>0.56	Indeterminate
Blood pressure (mm Hg [rest, max])		122/74, 140/80
Maximum $\dot{V}E$ (L/min)		29
Exercise breathing reserve (L/min)	>15	4
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	30.2	57.2
PaO_2 (mm Hg [rest, max ex])		58, 46
$P(A-a)O_2$ (mm Hg [rest, max ex])		41, 64
$PaCO_2$ (mm Hg [rest, max ex])		41, 41
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		8, 10
V_D/V_T (rest, heavy ex)		0.56, 0.55
HCO_3^- (mEq/L [rest, 2-min recov])		25, 24

Referring to Flowchart 5 (Fig. 8.5), V_D/V_T, $P(a - ET)CO_2$, and $P(A - a)O_2$ during exercise were all markedly abnormal (branch point 5.1). The breathing reserve was low (branch point 5.3). The breathing frequency was high even at rest and remained high at approximately 50 breaths per minute through the incremental exercise period (branch point 5.7). The maximum ventilation achieved approximated the patient's maximum ventilatory capacity. These findings indicate exercise limitation due to restrictive lung disease. Also consistent with this were the progressive decrease in PaO_2 and increase in $P(A - a)O_2$ as the work rate increased (Table 10.54.3 and see Fig. 10.54.1, panel 7). Another finding typical of restrictive lung disease was the high ratio of tidal volume to inspiratory capacity reached at the end of exercise (Fig. 10.54.1, panel 9). An abnormality in O_2 flow was also evident by the small rise in $\dot{V}O_2$ with increasing work rate and the failure of the O_2 pulse to rise (Fig. 10.54.1, panels 1 and 2, respectively) as the work rate was increased.

Conclusion

This test demonstrates ventilatory limitation to exercise in a patient with interstitial lung disease. Both reduced ventilatory capacity, due to pulmonary restriction, and increased ventilatory requirements, due to marked ventilation–perfusion mismatching, contributed to exercise limitation.

Table 10.54.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	122/74								7.44	25		48			37				
0.5	Rest		86	38	14.3	0.14	0.19	2.2	0.74			111			32			79	58	
1.0	Rest		89	36	15.2	0.18	0.23	2.6	0.78			113			32			67	53	
1.5	Rest		87	37	13.4	0.12	0.16	1.8	0.75			110			32			85	64	
2.0	Rest	119/71	90	36	15.0	0.17	0.22	2.4	0.77	7.40	25	109	58	41	33	41	8	70	54	0.56
2.5	Rest		89	39	15.5	0.15	0.20	2.2	0.75			111			32			81	61	
3.0	Rest		92	37	15.1	0.16	0.20	2.2	0.80			113			32			75	60	
3.5	Unloaded		92	42	18.3	0.24	0.31	3.4	0.77			108			36			61	48	
4.0	Unloaded		90	46	21.0	0.26	0.30	3.3	0.87			114			32			66	57	
4.5	Unloaded		92	51	23.4	0.29	0.35	3.8	0.83			113			32			66	54	
5.0	Unloaded		92	49	24.0	0.32	0.36	3.9	0.89			114			33			62	55	
5.5	Unloaded	126/71	93	48	24.1	0.33	0.37	4.0	0.89	7.41	26	115	52	53	32	41	9	61	54	0.54
6.0	Unloaded		95	50	24.3	0.30	0.33	3.5	0.91			117			31			67	61	
6.5	10		99	50	24.7	0.32	0.36	3.6	0.89			114			33			64	57	
7.0	10		97	51	25.0	0.32	0.36	3.7	0.89			114			33			65	57	
7.5	20		100	47	26.0	0.37	0.40	4.0	0.93			115			32			59	55	
8.0	20	137/74	105	47	25.8	0.37	0.40	3.8	0.93	7.41	25	116	49	58	32	40	8	59	55	0.54
8.5	30		104	49	28.6	0.43	0.46	4.4	0.93			118			31			57	53	
9.0	30		106	45	27.6	0.42	0.43	4.1	0.98			118			31			57	55	
9.5	40	140/80	108	45	29.1	0.44	0.42	3.9	1.05	7.39	24	120	46	64	31	41	10	57	60	0.55
10.0	Recovery		101	39	24.8	0.41	0.40	4.0	1.03			116			34			52	54	
10.5	Recovery		94	41	21.7	0.32	0.33	3.5	0.97			115			35			57	55	
11.0	Recovery		92	40	20.8	0.30	0.30	3.3	1.00			115			34			58	58	
11.5	Recovery	134/68	91	43	22.4	0.32	0.30	3.3	1.07	7.36	24	118	53	56	33	43	10	59	62	0.55
12.0	Recovery		91	43	17.8	0.16	0.15	1.6	1.07			122			30			88	94	

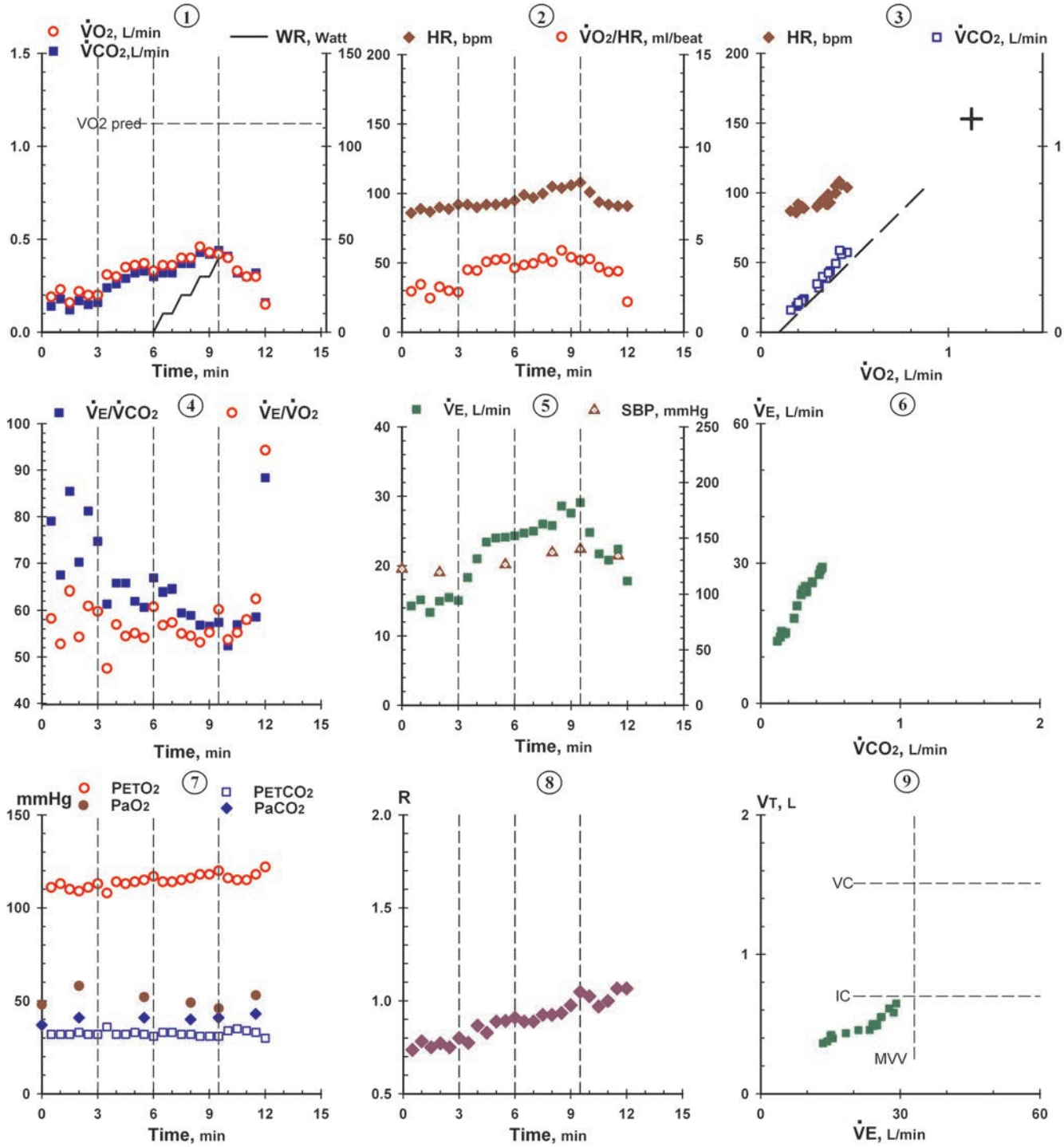

FIGURE 10.54.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 5 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 55 Idiopathic Interstitial Lung Disease

CLINICAL FINDINGS

This 45-year-old woman had a 6-month history of dyspnea, diffuse pulmonary infiltrates, and hypoxemia. She had been treated transiently with oral corticosteroids without lung biopsy or a specific diagnosis and without resolution of her disease. She had dyspnea after walking three blocks. She never smoked. She had worked in a pet shop so she had exposure to a variety of animals and birds and used bleach to clean cages. She had no other significant illnesses. She was referred for testing to characterize her degree of impairment.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. She pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 5 W per minute to her symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. Resting and exercise ECGs were normal. The patient stopped exercise because of leg fatigue. The O_2 saturation estimated by oximetry was 96% at rest and decreased to 93% at peak exercise.

Table 10.55.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		45
Sex		Female
Height (cm)		152
Weight (kg)	56	51
Hematocrit (%)		49
VC (L)	2.92	1.81
IC (L)	1.95	1.23
TLC (L)	4.29	3.62
FEV_1 (L)	2.41	1.42
FEV_1/VC (%)	83	78
MVV (L/min)	92	56
DLCO (mL/mm Hg/min)	22.7	4.3

$P(A-a)O_2$, $P(a-ET)CO_2$, and VD/VT calculated from arterial blood gas measures were abnormal.

INTERPRETATION

Comments

The resting respiratory studies show moderate restriction but extremely severe DLCO reduction (Table 10.55.1).

Analysis

The patient had a low peak $\dot{V}O_2$ and anaerobic threshold (Table 10.55.2). This leads from Flowchart 1 (Fig. 8.1) to Flowchart 4 (Fig. 8.4), where the negligible breathing

Table 10.55.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.44	0.88
Maximum heart rate (beats/min)	174	174
Maximum O_2 pulse (mL/beat)	8.3	5.1
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.7
AT (L/min)	>0.69	0.65
Blood pressure (mm Hg [rest, max])		150/90, 183/99
Maximum $\dot{V}E$ (L/min)		56
Exercise breathing reserve (L/min)	>15	0
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.3	35.2
PaO_2 (mm Hg [rest, max ex])		93, 74
$P(A-a)O_2$ (mm Hg [rest, max ex])		24, 50
$PaCO_2$ (mm Hg [rest, max ex])		33, 31
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		1, 5
VD/VT (rest, max ex)		0.31, 0.38
HCO_3^- (mEq/L [rest, 2-min recov])		23, 17

Table 10.55.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	150/84								7.42	23		80			36				
0.5	Rest		82	20	9.8	0.22	0.29	3.5	0.76			105			35			37	28	
1.0	Rest		83	22	8.5	0.16	0.18	2.2	0.89			107			35			41	37	
1.5	Rest		82	22	11.3	0.26	0.31	3.8	0.84			109			34			36	30	
2.0	Rest	150/90	86	23	11.6	0.23	0.23	2.7	1.00	7.45	23	116	93	24	32	33	1	42	42	0.31
2.5	Rest		88	21	11.4	0.24	0.23	2.6	1.04			117			31			40	42	
3.0	Rest		93	25	11.5	0.22	0.23	2.5	0.96			112			34			43	41	
3.5	Unloaded		105	25	15.7	0.33	0.31	3.0	1.06			119			30			41	44	
4.0	Unloaded		111	28	14.9	0.34	0.38	3.4	0.89			107			36			37	33	
4.5	Unloaded		114	28	17.2	0.42	0.48	4.2	0.88			109			35			35	31	
5.0	Unloaded		114	26	18.7	0.45	0.47	4.1	0.96			112			34			37	35	
5.5	Unloaded		117	26	2.7	0.50	0.52	4.4	0.96			113			33			37	36	
6.0	Unloaded	177/96	118	27	19.3	0.47	0.51	4.3	0.92	7.41	22	113	75	37	34	36	2	36	33	0.30
6.5	5		117	25	20.4	0.50	0.52	4.4	0.96			112			33			37	35	
7.0	5		120	27	21.3	0.51	0.53	4.4	0.96			114			33			37	36	
7.5	10		121	27	22.6	0.55	0.57	4.7	0.96			113			33			37	36	
8.0	10	177/96	124	29	22.5	0.53	0.55	4.4	0.96	7.41	21	114	75	40	32	34	2	38	36	0.29
8.5	15		128	29	24.1	0.58	0.59	4.6	0.98			116			32			37	37	
9.0	15		130	30	23.8	0.58	0.57	4.4	1.02			104			37			37	37	
9.5	20		139	28	24.6	0.64	0.65	4.7	0.98			110			36			35	34	
10.0	20	180/99	142	28	22.8	0.63	0.68	4.8	0.93	7.39	21	110	80	32	37	36	–1	32	30	0.23
10.5	25		145	36	33.0	0.80	0.74	5.1	1.08			113			36			37	40	
11.0	25		148	37	35.8	0.83	0.78	5.3	1.06			118			32			39	42	
11.5	30		151	36	32.8	0.79	0.71	4.7	1.11			118			33			38	42	
12.0	30	180/96	158	44	40.0	0.87	0.74	4.7	1.18	7.39	20	122	77	43	30	34	4	42	49	0.35
12.5	35		159	47	43.6	0.91	0.77	4.8	1.18			123			29			44	51	
13.0	35		165	46	43.8	0.90	0.77	4.7	1.17			123			28			44	52	
13.5	40		165	48	42.1	0.89	0.79	4.8	1.13			122			29			43	48	
14.0	40	180/96	168	48	46.6	0.95	0.82	4.9	1.16	7.39	19	123	74	47	28	32	4	45	52	0.36
14.5	45		171	49	49.0	0.98	0.83	4.9	1.18			124			28			46	54	
15.0	45	183/99	174	55	56.0	1.08	0.88	5.1	1.23	7.38	18	127	74	50	26	31	5	48	58	0.38
15.5	Recovery		169	40	43.2	0.92	0.79	4.7	1.16			128			28			43	50	
16.0	Recovery		163	41	40.9	0.82	0.64	3.9	1.28			126			27			46	58	
16.5	Recovery		153	30	23.4	0.61	0.53	3.5	1.15			121			30			34	39	
17.0	Recovery	165/90	146	28	24.6	0.53	0.46	3.2	1.15	7.35	17	122	98	24	29	31	2	42	48	0.30

reserve (branch point 4.1) and a high VD/VT (Table 10.55.3) (branch point 4.2) point to lung disease with impaired peripheral oxygenation. Consistent with this were the findings of a high VT/IC ratio, high breathing frequency, positive $P(a - ET)CO_2$, wide and increasing $P(A - a)O_2$, and a steep heart rate (HR) versus $\dot{V}O_2$ relationship. The $\Delta\dot{V}O_2/\Delta WR$ was within normal limits, but the low and unchanging O_2 pulse was striking (Fig. 10.55.1, panels 2 and 3). The decrease in PaO_2 and O_2 saturation was gradual and mild, so a right-to-left shunt was unlikely. Although oxygenation was abnormal, it was not abnormal enough to account for the O_2 flow disorder implied by the low O_2 pulse and steep HR response. Instead, the low, nonincreasing O_2 pulse probably reflects a low stroke volume secondary to pulmonary vascular disease.

Conclusion

This case is presented to show the effects on exercise of a severe pulmonary vascular occlusive defect accompanying interstitial lung disease. There was clear evidence of ventilatory limitation to exercise. However, circulatory impairment was also evident, likely due to the associated pulmonary vascular disease.

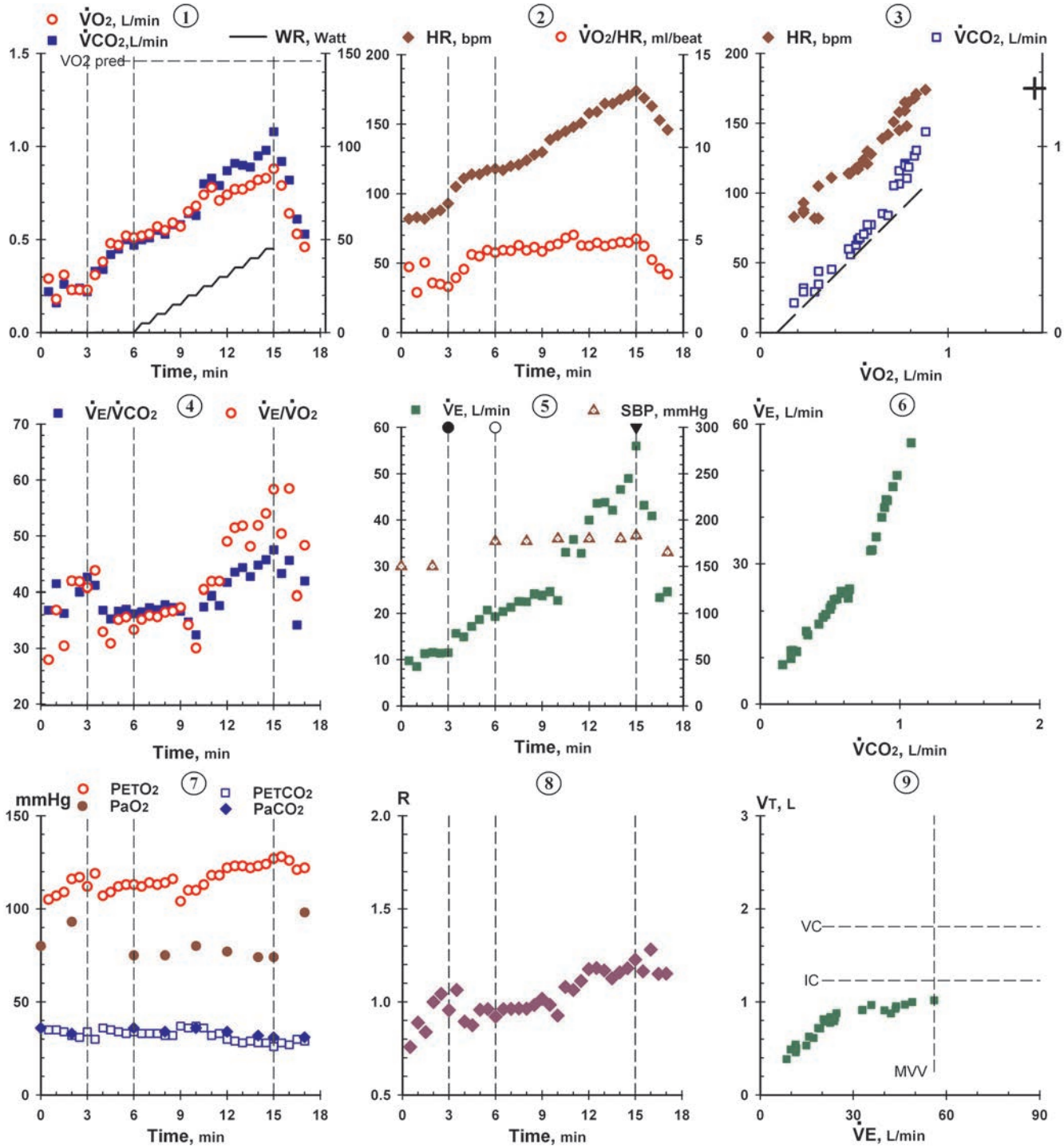

FIGURE 10.55.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 5 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 56 Interstitial Lung Disease

CLINICAL FINDINGS

This 20-year-old man with prior exposure to agricultural work and crop dusting chemicals was found to have an interstitial pneumonitis with mica deposits on lung biopsy. The patient noted severe dyspnea with walking one block or climbing two flights of stairs. He denied cough, wheezing, orthopnea, chest pain, syncope, peripheral edema, or cyanosis. An exercise test was performed to evaluate his response to an empiric trial of prednisone.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 10 W per minute to tolerance. Arterial blood was sampled every second minute, and intra-arterial pressure was recorded from a percutaneously placed brachial artery catheter. The patient was well-motivated and cooperative and stopped exercise because of fatigue and shortness of breath. No ECG abnormalities occurred at rest or during exercise, but a significant pulsus paradoxus (blood pressure variations with breathing) was noted during exercise.

INTERPRETATION

Comments

Resting respiratory function studies showed severe restrictive lung disease (Table 10.56.1). Arterial blood gases revealed a chronic, compensated respiratory acidosis with mild hypoxemia.

Table 10.56.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		20
Sex		Male
Height (cm)		160
Weight (kg)	66	48
Hematocrit (%)		51
VC (L)	3.52	1.21
IC (L)	2.37	0.74
FEV_1 (L)	2.99	1.21
FEV_1/VC (%)	85	97
MVV (L/min)	125	51

Analysis

Peak $\dot{V}O_2$ and the anaerobic threshold were both markedly reduced (Table 10.56.2). Proceeding from Flowchart 1 (Fig. 8.1) to Flowchart 4 (Fig. 8.4) through branch points 4.1 and 4.2 leads to lung disease with impaired peripheral oxygenation. We are prompted to verify other findings consistent with this in the pulmonary vascular disease box. The high breathing frequency, high ratio of tidal volume to inspiratory capacity (Fig. 10.56.1, panel 9), and the low breathing reserve are all typical of severe restrictive lung disease. The elevated V_D/V_T and

Table 10.56.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.46	0.74
Maximum heart rate (beats/min)	200	182
Maximum O_2 pulse (mL/beat)	12.3	4.1
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	4.2
AT (L/min)	>0.98	<0.55
Blood pressure (mm Hg [rest, max ex])[a]		118/81, 165–126/ 102–63
Maximum $\dot{V}E$ (L/min)		47
Exercise breathing reserve (L/min)	>15	4
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	24.4	30.1
PaO_2 (mm Hg [rest, max ex])		73, 85
$P(A-a)O_2$ (mm Hg [rest, max ex])		15, 36
$PaCO_2$ (mm Hg [rest, max ex])		46, 42
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		3, 4
V_D/V_T (rest, max ex)		0.37, 0.36
HCO_3^- (mEq/L [rest, 2-min recovery])		28, 14

[a]Ranges reflect pulsus paradox.

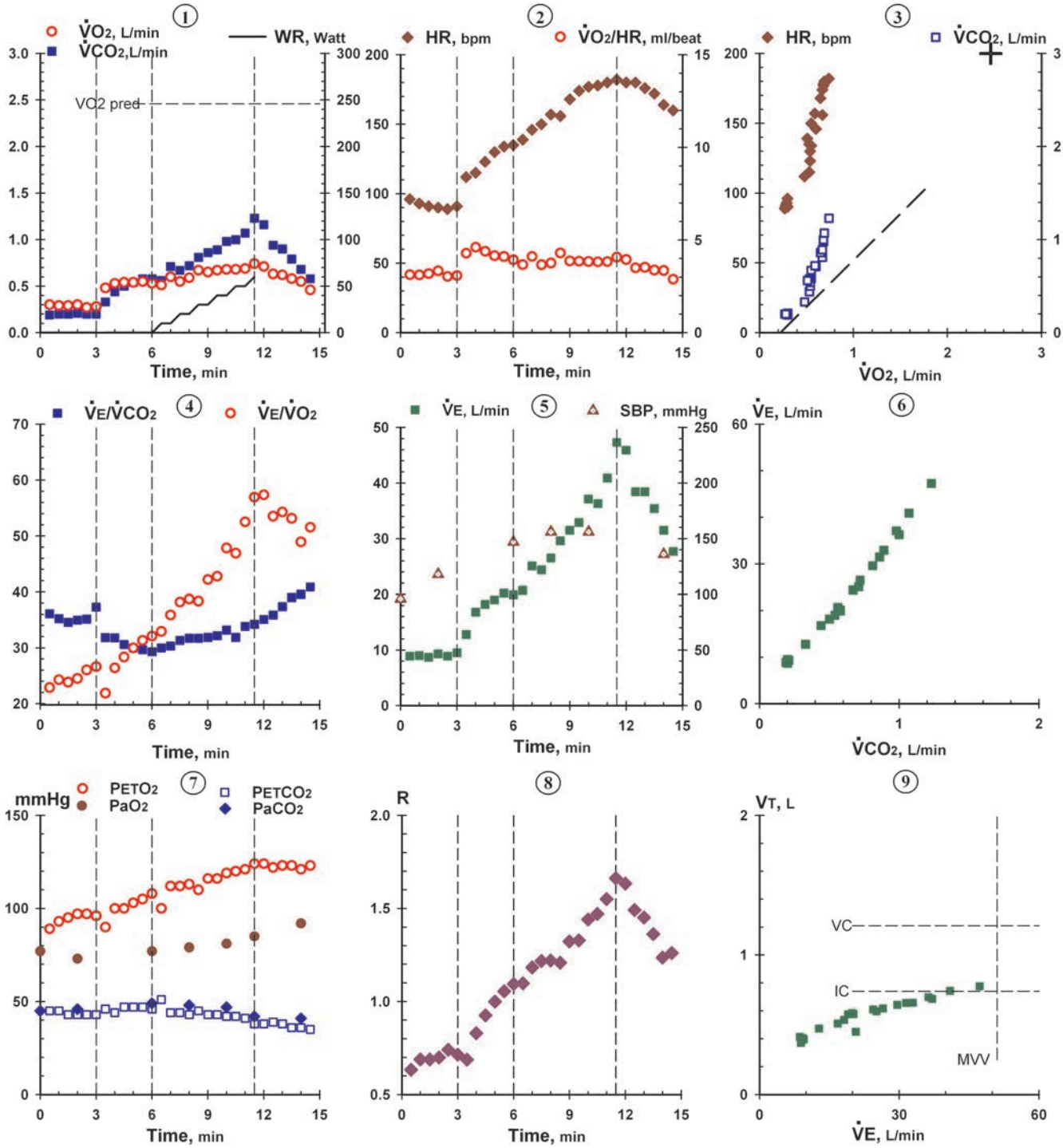

FIGURE 10.56.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.56.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
	Rest	96/68								7.40	27		77			45				
0.5	Rest		96	24	8.9	0.19	0.30	3.1	0.63			89			45			36	23	
1.0	Rest		93	23	9.0	0.20	0.29	3.1	0.69			93			45			35	24	
1.5	Rest		91	21	8.7	0.20	0.29	3.2	0.69			95			43			35	24	
2.0	Rest	118/81	90	23	9.3	0.21	0.30	3.3	0.70	7.40	28	97	73	15	43	46	3	35	24	0.37
2.5	Rest		89	22	8.9	0.20	0.27	3.0	0.74			97			43			35	26	
3.0	Rest		91	24	9.5	0.20	0.28	3.1	0.71			96			43			37	27	
3.5	Unloaded		112	27	12.8	0.33	0.48	4.3	0.69			90			46			32	22	
4.0	Unloaded		115	33	16.8	0.44	0.53	4.6	0.83			100			44			32	26	
4.5	Unloaded		123	34	18.2	0.50	0.54	4.4	0.93			100			47			31	28	
5.0	Unloaded		130	33	19.0	0.54	0.54	4.2	1.00			103			47			30	30	
5.5	Unloaded		134	35	20.2	0.58	0.55	4.1	1.05			105			47			30	31	
6.0	Unloaded	147/93	135	34	19.9	0.58	0.53	3.9	1.09	7.35	27	108	77	27	46	49	3	29	32	0.34
6.5	10		139	46	20.7	0.56	0.51	3.7	1.10			100			51			30	33	
7.0	10		146	42	25.1	0.71	0.60	4.1	1.18			112			44			30	36	
7.5	20		150	40	24.4	0.67	0.55	3.7	1.22			112			44			31	38	
8.0	20	156/96	157	43	26.5	0.72	0.59	3.8	1.22	7.33	25	113	79	30	43	48	5	32	39	0.37
8.5	30		156	46	29.6	0.81	0.67	4.3	1.21			110			45			32	38	
9.0	30		168	48	31.5	0.86	0.65	3.9	1.32			116			43			32	42	
9.5	40		174	50	32.9	0.89	0.67	3.9	1.33			116			43			32	43	
10.0	40	156/90	177	54	37.1	0.98	0.68	3.8	1.44	7.28	22	119	81	33	42	47	5	33	48	0.39
10.5	50		178	52	36.3	1.00	0.68	3.8	1.47			120			42			32	47	
11.0	50		180	55	40.9	1.07	0.69	3.8	1.55			121			41			34	53	
11.5	60	165–126/ 102–63	182	61	47.3	1.23	0.74	4.1	1.66	7.23	17	124	85	36	38	42	4	34	57	0.36
12.0	Recovery		180	61	45.9	1.16	0.71	3.9	1.63			124			38			35	57	
12.5	Recovery		180	55	38.4	0.94	0.63	3.5	1.49			122			39			36	54	
13.0	Recovery		176	56	38.4	0.90	0.62	3.5	1.45			123			38			37	54	
13.5	Recovery		172	54	35.4	0.79	0.58	3.4	1.36			123			36			39	53	
14.0	Recovery	136/69	164	54	31.5	0.68	0.55	3.4	1.24	7.15	14	121	92	23	36	41	5	40	49	0.40
14.5	Recovery		160	47	27.7	0.58	0.46	2.9	1.26			123			35			41	52	

positive $P(a - ET)CO_2$ (Table 10.56.3) indicate inadequate perfusion of ventilated air spaces.

In light of all these abnormalities, the lack of severe hypoxemia is remarkable but could be explained by normal red cell transit time through the pulmonary circulation. The extremely low O_2 pulse implies that stroke volume must be extremely low, and the cardiac output appears to be relatively fixed, as indicated by the failure of $\dot{V}O_2$ to increase despite the increasing work rate. Failure to increase cardiac output during exercise means that red blood cell pulmonary residence time could remain at resting levels, allowing time for equilibration of alveolar P_{O_2} with pulmonary capillary P_{O_2}. This may explain the absence of severe arterial hypoxemia. In contrast to $\dot{V}O_2$, there is a striking increase in $\dot{V}CO_2$ during exercise (Fig. 10.56.1, panel 1) resulting from the severe metabolic (lactic) acidosis that developed as a result of the impaired cardiac output response to exercise (arterial HCO_3^- decreased 14 mEq/L in 8 minutes).

Conclusion

This young man had extremely severe restrictive lung disease and secondary pulmonary vascular disease. As a result, he had high dead space ventilation and extremely low stroke volume and cardiac output but little arterial hypoxemia.

Case 57 Sarcoidosis

CLINICAL FINDINGS

This 39-year-old woman was referred for exercise testing with complaints of mild shortness of breath of 1 year's duration and diminished exercise tolerance of 18 months' duration. One year previously, following an episode of hepatitis, she was found to have a thin-walled cystic lesion in the right lower lung field without infiltrates or adenopathy. On follow-up studies, the cyst was found to be enlarging and was therefore surgically resected. Preoperative exercise testing suggested cardiovascular limitation prompting monitoring during surgery of pulmonary artery pressures, which were normal. The resected lesion was found to contain noncaseating granulomata compatible with sarcoidosis; stains and cultures for organisms were negative. The patient had never smoked cigarettes and took no medications. The test presented here is a postoperative exercise test conducted with an intra-arterial catheter to follow up the prior findings in more detail.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. She pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 15 W per minute to tolerance. Arterial blood was sampled every second minute, and intra-arterial pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of lightheadedness and shortness of breath. No ECG abnormalities occurred at rest or during exercise.

Table 10.57.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		39
Sex		Female
Height (cm)		162
Weight (kg)	63	68
Hematocrit (%)		41
VC (L)	3.38	2.89
IC (L)	2.25	1.80
TLC (L)	5.84	4.34
FEV_1 (L)	2.75	2.40
FEV_1/VC (%)	81	88
MVV (L/min)	105	98
DLCO (mL/mm Hg/min)	24.2	17.9

INTERPRETATION

Comments

The resting respiratory function studies were similar to her prelung resection values and showed mild restrictive lung disease (Table 10.57.1).

Analysis

The patient was cooperative with the study and developed a significant lactic acidosis as reflected in the end-exercise R of 1.2 (Fig. 10.57.1, panel 8). Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ and the anaerobic threshold were both decreased (Table 10.57.2), leading through branch

Table 10.57.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.70	1.12
Maximum heart rate (beats/min)	181	173
Maximum O_2 pulse (mL/beat)	9.4	6.5
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	7.3
AT (L/min)	>0.81	<0.65
Blood pressure (mm Hg [rest, max])		146/88, 189/105
Maximum $\dot{V}E$ (L/min)		55
Exercise breathing reserve (L/min)	>15	43
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.3	31.5
PaO_2 (mm Hg [rest, max ex])		104, 119
$P(A-a)O_2$ (mm Hg [rest, max ex])		7, 7
$PaCO_2$ (mm Hg [rest, max ex])		32, 28
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		0, −4
VD/VT (rest, max ex)		0.30, 0.19
HCO_3^- (mEq/L [rest, 2-min recov])		22, 13

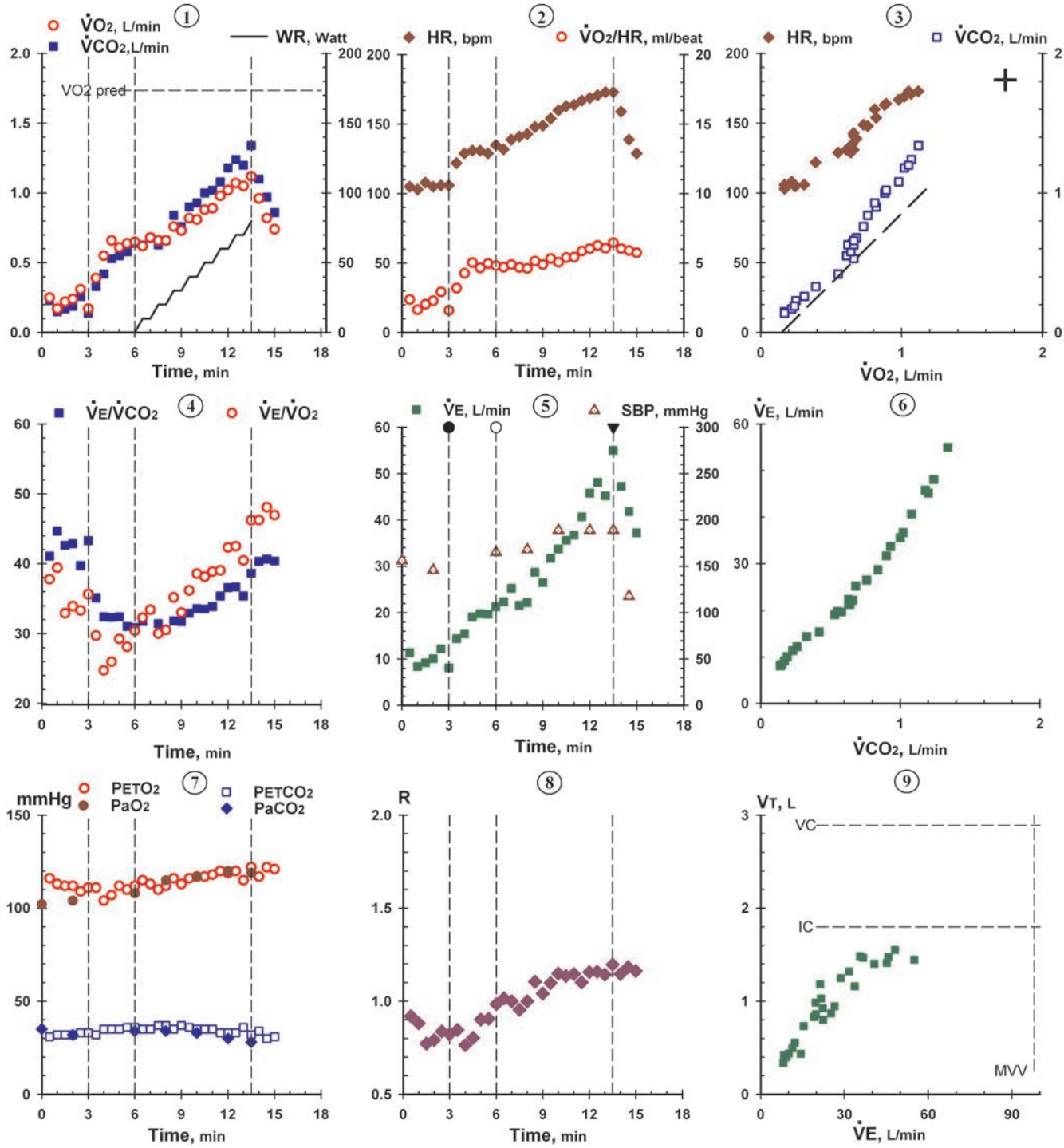

FIGURE 10.57.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.57.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	156/90								7.41	22		102			35				
0.5	Rest		105	23	11.4	0.23	0.25	2.4	0.92			116			31			41	38	
1.0	Rest		103	20	8.4	0.15	0.17	1.7	0.88			113			32			45	39	
1.5	Rest		108	23	9.2	0.17	0.22	2.0	0.77			112			32			43	33	
2.0	Rest	146/88	105	23	10.1	0.19	0.24	2.3	0.79	7.43	21	112	104	7	32	32	0	43	34	0.30
2.5	Rest		106	22	12.2	0.26	0.31	2.9	0.84			109			33			40	33	
3.0	Rest		106	24	8.1	0.14	0.17	1.6	0.82			111			33			43	36	
3.5	Unloaded		122	33	14.4	0.33	0.39	3.2	0.85			111			32			35	30	
4.0	Unloaded		129	21	15.4	0.42	0.55	4.3	0.76			104			35			32	25	
4.5	Unloaded		131	23	19.1	0.53	0.66	5.0	0.80			107			35			32	26	
5.0	Unloaded		131	23	19.8	0.55	0.61	4.7	0.90			112			35			32	29	
5.5	Unloaded		129	20	19.7	0.58	0.64	5.0	0.91			110			36			31	28	
6.0	Unloaded	165/99	135	18	21.3	0.64	0.65	4.8	0.98	7.39	20	112	108	8	36	34	–2	31	30	0.17
6.5	10		132	28	22.4	0.63	0.62	4.7	1.02			115			35			32	32	
7.0	10		139	29	25.2	0.68	0.68	4.9	1.00			113			35			33	33	
7.5	20		141	21	21.6	0.63	0.66	4.7	0.95			110			37			31	30	
8.0	20	168/97	143	24	22.2	0.66	0.66	4.6	1.00	7.38	20	112	115	1	37	34	–3	31	31	0.15
8.5	30		148	23	28.7	0.84	0.76	5.1	1.11			116			35			32	35	
9.0	30		149	28	26.5	0.76	0.73	4.9	1.04			113			37			32	33	
9.5	40		154	24	31.7	0.90	0.82	5.3	1.10			116			36			33	36	
10.0	40	189/105	160	29	33.7	0.93	0.81	51	1.15	7.37	19	117	117	3	35	33	–2	34	39	0.21
10.5	50		163	24	35.6	1.00	0.88	5.4	1.14			117			35			34	38	
11.0	50		164	25	36.7	1.02	0.89	5.4	1.15			118			35			34	39	
11.5	60		167	29	40.7	1.08	0.98	5.9	1.10			120			33			35	39	
12.0	60	189/105	169	31	45.8	1.18	1.02	6.0	1.16	7.35	16	119	120	3	33	30	–3	37	42	0.20
12.5	70		171	31	48.1	1.24	1.07	6.3	1.16			120			33			37	42	
13.0	70		173	32	45.2	1.20	1.05	6.1	1.14			115			36			35	40	
13.5	80	189/105	173	38	55.0	1.34	1.12	6.5	1.20	7.32	14	122	119	7	32	28	–4	39	46	0.19
14.0	Recovery		159	33	47.2	1.10	0.96	6.0	1.15			117			34			40	46	
14.5	Recovery	118/60	139	28	41.8	0.97	0.82	5.9	1.18			122			30			41	48	
15.0	Recovery		129	29	37.2	0.86	0.74	5.7	1.16			121			31			40	47	

point 1.3 to Flowchart 4 (Fig. 8.4). The breathing reserve was high (branch point 4.1). The mildly elevated ventilatory equivalents were accounted for by a low Pa_{CO_2} as V_D/V_T and $P(a - ET)_{CO_2}$ were normal (Table 10.57.3). The $P(A - a)_{O_2}$ values (branch point 4.3) were also normal, indicating uniform ventilation–perfusion ratios. This then implies an O_2 flow problem of nonpulmonary origin. The hematocrit was normal (branch point 4.4); however, the maximum O_2 pulse was extremely low and increased minimally as the work rate was increased. These findings suggest (branch point 4.6) impairment due to heart disease. There were no ECG findings to suggest coronary disease, and pulmonary vascular pressures measured previously were normal. Therefore, the findings were felt to be most compatible with cardiac sarcoidosis. An alternative consideration would be sarcoidosis affecting skeletal muscle.

Conclusion

Although resting pulmonary function tests demonstrated mild-to-moderate abnormalities due to pulmonary sarcoidosis, she was not limited by lung mechanics, nor were indices of pulmonary gas exchange abnormal. The exercise impairment instead reflected a pattern consistent with a defect in O_2 transport, such as in systolic dysfunction, or in O_2 utilization at the muscle.

Case 58 Interstitial Pneumonitis: Before and after Corticosteroid Therapy

CLINICAL FINDINGS

This 37-year-old housewife developed progressive shortness of breath and was found to have interstitial lung disease on chest imaging studies. She did not consent to lung biopsy and instead underwent an empiric trial of corticosteroid therapy. She underwent exercise testing for objective assessment of her functional impairment before and after treatment.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. She pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 15 W per minute to her symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. Her resting and exercise ECGs were normal. In the initial study, she stopped exercise because of shortness of breath. Testing was repeated 6 months later while taking 30 mg prednisone daily. She was asymptomatic at the time of the second test.

INTERPRETATION

Comments

The resting respiratory function studies indicate that this patient had severe restrictive lung disease before therapy, which improved markedly after therapy (Table 10.58.1). The resting ECG was normal.

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and the anaerobic threshold were both abnormal (Table 10.58.2). Referring to Flowchart 4 (Fig. 8.4), the breathing reserve was low (branch point 4.1). V_D/V_T was high (branch point 4.2). This leads to the category of lung disease with an O_2 flow problem. Consistent with her restrictive lung disease were the high V_T/IC ratio (Fig. 10.58.1, panel 9), breathing frequency exceeding 50 breaths per minute at the maximum work rate (Table 10.58.3), a $P(A - a)O_2$ that increased and a PaO_2 that decreased systematically with work rate, and increased values of $P(a - ET)CO_2$ and V_D/V_T (see Table 10.58.3).

After treatment, the peak $\dot{V}O_2$ improved significantly and exceeded the predicted value (Table 10.58.4). Arterial

Table 10.58.1

Selected Respiratory Function Data

Measurement	Predicted	Before treatment	After treatment
Age (years)		37	
Sex		Female	
Height (cm)		168	
Weight (kg)	66	57	
Hematocrit (%)		42	
VC (L)	3.76	1.71	3.85
IC (L)	2.50	1.31	2.25
FEV_1 (L)	3.08	1.52	3.10
FEV_1/VC (%)	82	89	81
MVV (L/min)	120	66	130
D_{LCO} (mL/mm Hg/min)	28.5	16.2	

Table 10.58.2

Selected Exercise Data

Measurement	Predicted	Before treatment	After treatment
Peak $\dot{V}O_2$ (L/min)	1.72	1.35	2.01
Maximum heart rate (beats/min)	183	149	174
Maximum O_2 pulse (mL/beat)	9.4	9.1	11.6
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	9.5	9.8
AT (L/min)	>0.79	0.80	1.0
Blood pressure (mm Hg [rest, max])		119/68, 190/81	125/75, 181/88
Maximum $\dot{V}E$ (L/min)		58	86
Exercise breathing reserve (L/min)	>15	8	44
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.8	34.4	25.7
PaO_2 (mm Hg [rest, max ex])		65, 51	117, 98
$P(A-a)O_2$ (mm Hg [rest, max ex])		43, 65	–1, 26
$PaCO_2$ (mm Hg [rest, max ex])		36, 36	29, 31
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		3, 3	–3, –2
V_D/V_T (rest, heavy ex)		0.40, 0.32	0.22, 0.15
HCO_3^- (mEq/L [rest, 2-min recov])		25, 21	24, 15

hypoxemia did not occur with exercise and $P(a-ET)CO_2$ and V_D/V_T were normal, indicating that the ventilation–perfusion abnormality observed before treatment had been corrected. Moreover, the breathing pattern no longer had the characteristic pattern of restriction observed during pretreatment exercise (compare panels 9 of Figs. 10.58.1 and 10.58.2).

Conclusion

The patient is considered to have reduced exercise capacity due to interstitial lung disease. This case is presented to show the remarkable reversal of ventilatory limitation and gas exchange abnormalities after 6 months of treatment.

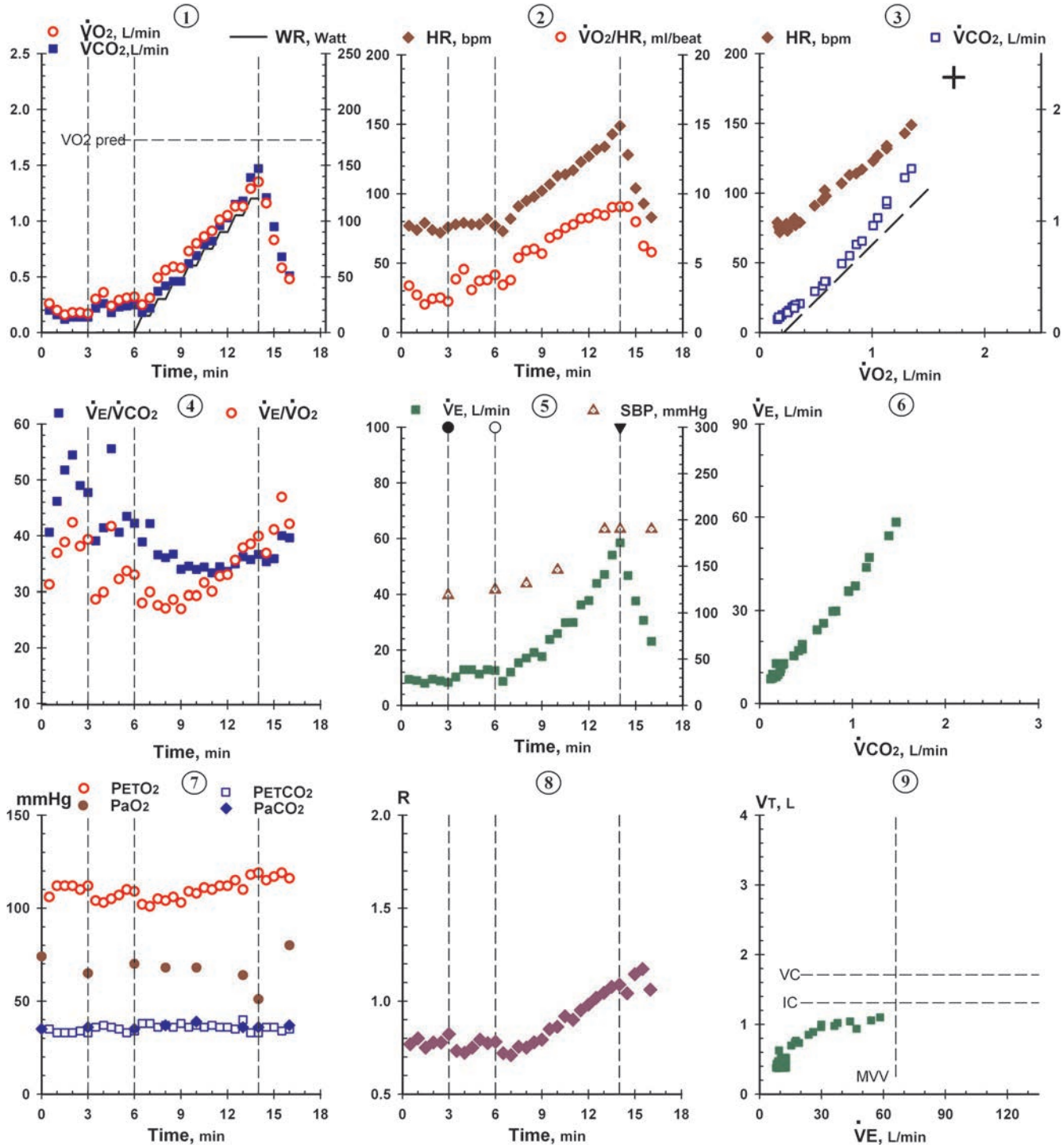

FIGURE 10.58.1. Pretreatment test. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.58.3

Before Treatment

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	*a*	*(A − a)*	*ET*	*a*	*(a − ET)*			
	Rest									7.47	25		74			35				
0.5	Rest		77	15	9.4	0.20	0.26	3.4	0.77			106			35			41	31	
1.0	Rest		74	19	9.0	0.16	0.20	2.7	0.80			112			33			46	37	
1.5	Rest		79	21	8.0	0.12	0.16	2.0	0.75			112			33			52	39	
2.0	Rest		74	22	9.5	0.14	0.18	2.4	0.78			112			33			55	42	
2.5	Rest		72	24	8.9	0.14	0.18	2.5	0.78			110			34			49	38	
3.0	Rest	119/68	76	19	8.3	0.14	0.17	2.2	0.82	7.45	25	112	65	43	33	36	3	48	39	0.40
3.5	Unloaded		78	20	10.3	0.22	0.30	3.8	0.73			104			36			39	29	
4.0	Unloaded		79	25	12.9	0.26	0.36	4.6	0.72			103			37			41	30	
4.5	Unloaded		78	34	12.9	0.18	0.24	3.1	0.75			105			36			56	42	
5.0	Unloaded		78	23	11.3	0.23	0.29	3.7	0.79			107			35			41	32	
5.5	Unloaded		82	29	12.9	0.24	0.31	3.8	0.77			110			33			43	34	
6.0	Unloaded	125/68	77	24	12.6	0.25	0.32	4.2	0.78	7.44	23	109	70	37	34	35	1	42	33	0.35
6.5	15		73	20	8.7	0.18	0.25	3.4	0.72			102			38			39	28	
7.0	15		82	32	12.0	0.22	0.31	3.8	0.71			101			38			42	30	
7.5	30		91	22	15.4	0.37	0.49	5.4	0.76			105			36			37	28	
8.0	30	131/68	95	23	17.1	0.42	0.56	5.9	0.75	7.44	25	104	68	35	37	37	0	36	27	0.31
8.5	45		98	26	19.1	0.46	0.59	6.0	0.78			106			36			37	29	
9.0	45		102	23	17.6	0.46	0.58	5.7	0.79			103			38			34	27	
9.5	60		107	28	23.8	0.62	0.73	6.8	0.85			109			36			35	29	
10.0	60	146/75	113	29	25.9	0.69	0.80	7.1	0.86	7.43	25	108	68	38	37	39	2	34	29	0.32
10.5	75		114	31	29.8	0.79	0.86	7.5	0.92			111			36			34	32	
11.0	75		117	30	29.9	0.82	0.91	7.8	0.90			110			37			33	30	
11.5	90		123	37	36.2	0.96	1.01	8.2	0.95			112			36			34	33	
12.0	90		127	37	37.8	1.03	1.05	8.3	0.98			112			36			34	33	
12.5	105		132	42	43.8	1.15	1.13	8.6	1.02			115			35			35	36	
13.0	105	190/78	134	50	47.0	1.18	1.13	8.4	1.04	7.42	23	110	64	51	40	36	−4	36	38	0.31
13.5	120		143	51	54.0	1.39	1.29	9.0	1.08			118			33			36	39	
14.0	120	190/81	149	53	58.4	1.47	1.35	9.1	1.09	7.41	22	119	51	65	33	36	3	37	40	0.32
14.5	Recovery		128	45	46.6	1.21	1.16	9.1	1.04			115			36			35	37	
15.0	Recovery		104	41	37.6	0.95	0.83	8.0	1.14			117			36			36	41	
15.5	Recovery		93	41	30.7	0.68	0.58	6.2	1.17			119			34			40	47	
16.0	Recovery	190/81	83	34	23.1	0.51	0.48	5.8	1.06	7.36	21	116	80	35	35	37	2	40	42	0.36

Table 10.58.4

After Treatment

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	125/75								7.45	23		94			34				
0.5	Rest		80	15	7.7	0.21	0.23	2.9	0.91			112			34			31	28	
1.0	Rest		78	11	6.8	0.17	0.19	2.4	0.89			115			32			35	31	
1.5	Rest		84	13	7.1	0.16	0.19	2.3	0.84			112			33			37	32	
2.0	Rest		83	24	8.2	0.13	0.15	1.8	0.87			115			31			47	41	
2.5	Rest		85	13	10.7	0.25	0.27	3.2	0.98			115			31			38	36	
3.0	Rest	119/75	84	19	7.8	0.15	0.18	2.1	0.83	7.50	22	113	117	–1	32	29	–3	41	34	0.22
3.5	Unloaded		89	28	8.7	0.21	0.31	3.5	0.68			94			39			30	20	
4.0	Unloaded		90	16	4.6	0.09	0.17	1.9	0.53			83			40			36	19	
4.5	Unloaded		97	20	9.2	0.24	0.34	3.5	0.71			99			38			31	22	
5.0	Unloaded		88	15	12.8	0.37	0.51	5.8	0.73			100			38			31	23	
5.5	Unloaded		87	14	10.1	0.32	0.47	5.4	0.68			98			37			28	19	
6.0	Unloaded	125/75	85	14	8.0	0.24	0.37	4.4	0.65	7.43	25	94	93	3	39	38	–1	28	18	0.17
6.5	15		88	21	6.9	0.21	0.34	3.9	0.62			88			42			24	15	
7.0	15		89	23	7.5	0.21	0.33	3.7	0.64			90			41			26	17	
7.5	30		95	14	11.5	0.39	0.58	6.1	0.67			92			41			26	18	
8.0	30	125/69	95	12	14.1	0.49	0.67	7.1	0.73	7.44	25	97	94	8	39	37	–2	27	20	0.12
8.5	45		104	15	15.9	0.58	0.81	7.8	0.72			94			41			25	18	
9.0	45		109	17	19.2	0.66	0.84	7.7	0.79			99			40			27	21	
9.5	60		112	14	20.4	0.76	0.95	8.5	0.80			100			41			25	20	
10.0	60	144/75	114	15	23.3	0.87	1.01	8.9	0.86	7.43	25	103	99	8	40	38	–2	25	22	0.10
10.5	75		122	18	23.1	0.87	1.06	8.7	0.82			99			43			25	20	
11.0	75		126	16	25.3	0.93	1.03	8.2	0.90			103			41			26	23	
11.5	90		128	22	32.6	1.14	1.28	10.0	0.89			100			43			27	24	
12.0	90	156/75	133	16	30.3	1.17	1.24	9.3	0.94	7.42	24	106	84	26	42	38	–4	25	23	0.08
12.5	105		138	20	37.2	1.36	1.39	10.1	0.98			109			40			26	26	
13.0	105		145	20	41.4	1.50	1.47	10.1	1.02			106			42			26	27	
13.5	120		148	22	45.8	1.65	1.59	10.7	1.04			111			40			27	28	
14.0	120	181/81	152	22	49.4	1.77	1.66	10.9	1.07	7.40	24	112	95	18	39	39	0	27	29	0.17
14.5	135		160	25	55.0	1.88	1.70	10.6	1.11			115			37			28	31	
15.0	135		161	27	61.2	2.04	1.79	11.1	1.14			116			37			29	33	
15.5	130		167	29	71.7	2.27	1.89	11.3	1.20			118			36			31	37	
16.0	130	181/88	174	38	85.6	2.49	2.01	11.6	1.24	7.40	19	122	98	26	33	31	–2	33	41	0.15
16.5	Recovery		160	30	66.5	2.08	1.64	10.3	1.27			120			35			31	39	
17.0	Recovery		146	22	46.9	1.42	0.96	6.6	1.48			123			35			32	47	
17.5	Recovery		143	23	31.3	0.90	0.63	4.4	1.43			122			34			33	47	
18.0	Recovery	181/81	126	26	31.4	0.85	0.64	5.1	1.33	7.36	17	124	101	25	32	30	–2	34	46	0.15
18.5	Recovery		118	24	22.0	0.62	0.52	4.4	1.19			118			34			32	38	
19.0	Recovery	175/75	113	23	22.2	0.58	0.48	4.2	1.21	7.36	17	123	93	30	31	31	0	35	42	0.18

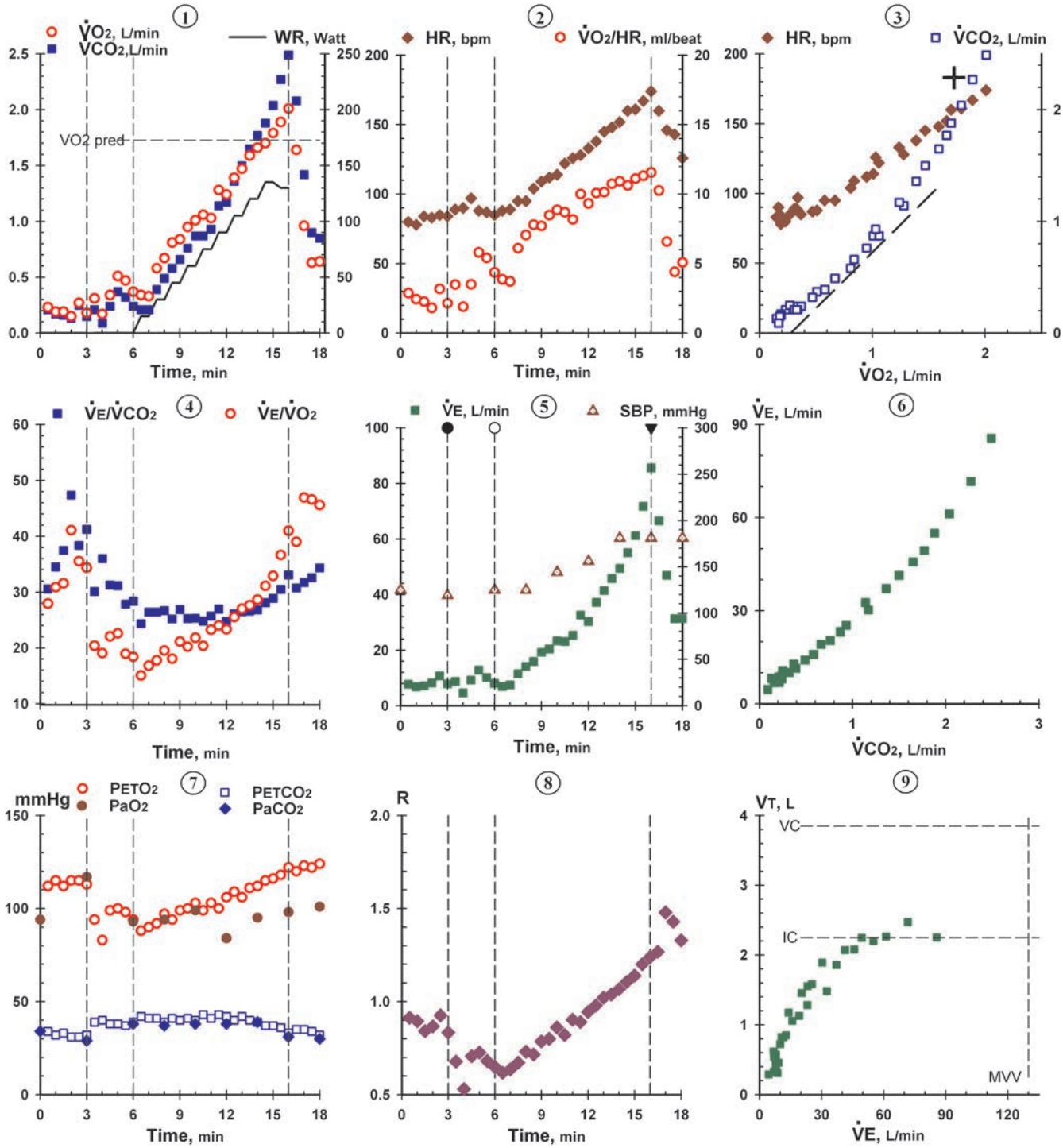

FIGURE 10.58.2. Posttreatment test. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 59 Interstitial Pulmonary Fibrosis: Air and Oxygen Breathing Studies

CLINICAL FINDINGS

This 47-year-old man had developed exertional dyspnea 12 years previously. A histologic diagnosis of pulmonary alveolar proteinosis was then made by open lung biopsy. Following whole-lung lavage, he was asymptomatic for approximately 10 years, but 10 months prior to evaluation, he became aware of progressive exertional dyspnea, first evident while skiing at high altitudes. Although previously active in sports, at the time of testing, he was unable to walk more than 30 yards on flat ground at a normal pace. He coughed with exercise and sometimes produced clear sputum. He denied smoking, wheezing, or edema. The results of his examination were normal except for digital clubbing and fine inspiratory rales at the lung bases. Chest radiographs showed increased interstitial markings with honeycombing.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer breathing room air and, after a 30-minute rest, repeated the test breathing 100% oxygen. On both tests, he pedaled at 60 rpm without added load for 3 minutes. The work rate was increased 15 W every minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. When breathing room air, he stopped exercise because of fatigue and lightheadedness. When breathing oxygen, he stopped because of leg pain and general fatigue. Resting and exercise ECGs were normal.

Table 10.59.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		47
Sex		Male
Height (cm)		174
Weight (kg)	77	85
Hematocrit (%)		41
VC (L)	4.49	2.20
IC (L)	2.99	1.14
TLC (L)	6.48	3.17
FEV_1 (L)	3.58	2.01
FEV_1/VC (%)	80	91
MVV (L/min, direct)	151	112
MVV (L/min, indirect)	143	80
D_{LCO} (mL/mm Hg/min)	30.7	13.9

INTERPRETATION

Comments

The resting pulmonary function studies demonstrated a severe restrictive disorder, with no evidence of airflow obstruction (Table 10.59.1). The resting ECG was normal.

Analysis

Referring to Flowchart 1 (Fig. 8.1), on the air breathing study, the peak $\dot{V}O_2$ and anaerobic threshold were reduced (Table 10.59.2). Referring to Flowchart 4 (Fig. 8.4), the breathing reserve was reduced (branch point 4.1). Following the low breathing reserve branch to branch point 4.2, the high V_D/V_T leads to lung disease with impaired oxygenation. Additional findings consistent with this condition include (1) the high V_T/IC ratio (Fig. 10.59.1, panel 9); (2) the low and progressively decreasing PaO_2 as work rate increased (Fig. 10.59.1, panel 7); (3) the high breathing frequency at the peak $\dot{V}O_2$ (see Table 10.59.3); (4) the increased $P(a - ET)CO_2$ (Fig. 10.59.1, panel 7); (5) steep heart rate response relative to increasing $\dot{V}O_2$ (Fig. 10.59.1, panel 3); (6) low O_2 pulse, which fails to increase as the work rate increased (Fig. 10.59.1, panel 2); (7) reduced $\Delta\dot{V}O_2/\Delta WR$ (see Table 10.59.2 and Fig. 10.59.1, panel 1); and (8) progressive elevation of $P(A - a)O_2$ (Table 10.59.3). All of these findings are characteristic of restrictive interstitial lung disease.

Breathing O_2 allowed the patient to increase his maximum work rate from 90 to 135 W (Table 10.59.4 and Fig. 10.59.2). This was accomplished primarily because of a decreased ventilatory drive. In contrast to regulating arterial PCO_2 around 40 as the patient did when breathing air, 100% O_2 breathing attenuated ventilatory drive (via carotid body inhibition), reflected in lower breathing frequency. The reduction in ventilation caused acute respiratory acidosis, with exercise $PaCO_2$ increasing to 64 mm Hg. The patient was no longer hypoxemic with exercise and was less dyspneic. The reduction in ventilation was also associated with lower ventilatory equivalent values on the O_2 breathing test (see Table 10.59.2 and Figs. 10.59.1 and 10.59.2, panel 4). The calculated V_D/V_T values were similarly high on both

Table 10.59.2

Selected Exercise Data

Measurement	Predicted	Room air	Oxygen
Peak $\dot{V}O_2$ (L/min)	2.60	1.23	
Maximum heart rate (beats/min)	173	150	154
Maximum O_2 pulse (mL/beat)	15.0	8.2	
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.6	
AT (L/min)	>1.12	0.85	
Blood pressure (mm Hg [rest, max])		120/75, 175/84[a]	138/87, 195/90[a]
Maximum $\dot{V}E$ (L/min)		72	56
Exercise breathing reserve (L/min)	>15	8	32
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.7	48.1	33.7
PaO_2 (mm Hg [rest, max ex])		62, 37	568, 284
$P(A-a)O_2$ (mm Hg [rest, max ex])		30, 73	102, 365
$PaCO_2$ (mm Hg [rest, max ex])		40, 44	43, 64
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		6, 10	4, 12
V_D/V_T (rest, heavy ex)		0.54, 0.54	0.51, 0.56
HCO_3^- (mEq/L [rest, 2-min recov])		23, 20	26, 22

[a]Systolic pulses paradoxus of 70 mm Hg.

tests, however, as O_2 breathing did not fundamentally alter the abnormalities in pulmonary gas exchange.

Conclusion

The patient had severe interstitial lung disease, with an O_2 flow problem attributable to a combination of arterial hypoxemia and pulmonary vascular disease. Breathing O_2 attenuated his ventilatory drive and provided relief of dyspnea. This case is presented to illustrate two major findings: (1) the progressive arterial hypoxemia typical of pulmonary fibrosis, and (2) the role of the carotid bodies in ventilatory drive in the presence of arterial hypoxemia.

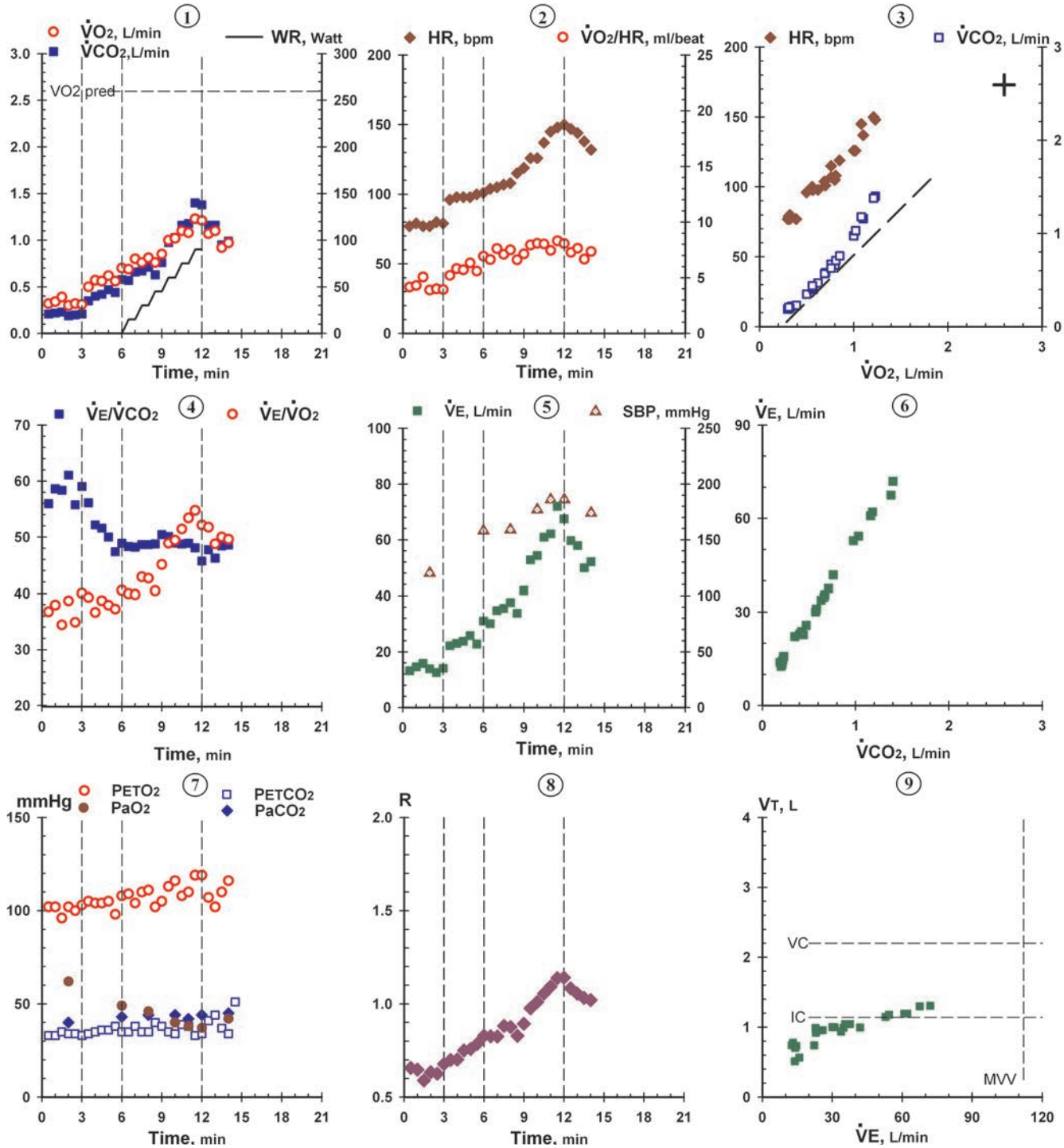

FIGURE 10.59.1. Air breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.59.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest		77	17	13.2	0.21	0.32	4.2	0.66			102			33			56	37	
1.0	Rest		79	20	14.6	0.22	0.34	4.3	0.65			102			33			59	38	
1.5	Rest		77	28	15.8	0.23	0.39	5.1	0.59			96			35			58	34	
2.0	Rest	120/75	77	27	13.9	0.19	0.30	3.9	0.63	7.37	23	102	62	30	34	40	6	61	39	0.54
2.5	Rest		80	17	12.6	0.20	0.32	4.0	0.63			100			34			56	35	
3.0	Rest		79	20	14.1	0.21	0.31	3.9	0.68			103			33			59	40	
3.5	Unloaded		96	30	22.2	0.35	0.50	5.2	0.70			105			34			56	39	
4.0	Unloaded		98	25	23.0	0.40	0.57	5.8	0.70			104			35			52	37	
4.5	Unloaded		98	25	23.8	0.42	0.56	5.7	0.75			104			36			52	39	
5.0	Unloaded		98	27	25.8	0.47	0.62	6.3	0.76			105			36			50	38	
5.5	Unloaded		100	23	22.8	0.44	0.56	5.6	0.79			98			38			47	37	
6.0	Unloaded	158/81	101	31	31.0	0.58	0.70	6.9	0.83	7.35	23	108	49	51	35	43	8	49	41	0.54
6.5	15		104	30	30.1	0.57	0.69	6.6	0.83			109			35			48	40	
7.0	15		105	35	34.8	0.66	0.80	7.6	0.83			104			38			48	40	
7.5	30		107	34	35.5	0.67	0.76	7.1	0.88			110			35			49	43	
8.0	30	159/75	108	36	37.6	0.71	0.81	7.5	0.88	7.34	23	111	46	55	35	44	9	49	43	0.55
8.5	45		115	36	33.8	0.63	0.76	6.6	0.83			102			40			49	40	
9.0	45		119	42	41.9	0.76	0.85	7.1	0.89			105			38			50	45	
9.5	60		126	46	52.8	0.98	1.00	7.9	0.98			113			35			50	49	
10.0	60	177/90	126	46	54.3	1.03	1.02	8.1	1.01	7.33	23	116	40	66	34	44	10	49	49	0.56
10.5	75		137	51	60.9	1.16	1.10	8.0	1.05			108			39			49	51	
11.0	75	186/90	145	52	62.1	1.18	1.08	7.4	1.09	7.33	22	110	38	73	38	42	4	49	53	0.54
11.5	90		148	55	72.0	1.40	1.23	8.3	1.14			119			33			48	55	
12.0	90	186/93	150	52	67.5	1.38	1.21	8.1	1.14	7.31	22	119	37	73	34	44	10	46	52	0.53
12.5	Recovery		147	51	59.7	1.16	1.07	7.3	1.08			107			41			48	52	
13.0	Recovery		144	50	57.9	1.16	1.10	7.6	1.05			102			44			46	49	
13.5	Recovery		138	46	49.9	0.95	0.92	6.7	1.03			110			37			48	50	
14.0	Recovery	174/90	132	47	52.1	0.99	0.97	7.3	1.02	7.27	20	116	42	64	34	45	11	49	50	0.56

Table 10.59.4

Oxygen Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	Po_2, mm Hg			Pco_2, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	132/84								7.44	24		66			36				
0.5	Rest		94	21	11.6	0.19									40			52		
1.0	Rest		93	19	12.1	0.18									39			58		
1.5	Rest		90	23	13.3	0.21									37			54		
2.0	Rest	138/87	91	29	14.5	0.23				7.39	26		568	102	39	43	4	52		0.51
2.5	Rest		92	23	14.5	0.22									38			57		
3.0	Rest		96	25	14.0	0.18									36			66		
3.5	Rest		96	22	17.8	0.30									37			53		
4.0	Rest		89	30	16.7	0.24									37			59		
4.5	Unloaded		102	28	19.8	0.33									37			53		
5.0	Unloaded		100	26	20.1	0.34									39			53		
5.5	Unloaded		100	25	18.9	0.33									39			51		
6.0	Unloaded		100	21	15.7	0.31									45			45		
6.5	Unloaded		104	22	16.4	0.37									45			39		
7.0	Unloaded	192/108	114	24	17.2	0.42				7.33	26		540	122	46	51	5	36		0.47
7.5	15		122	22	16.9	0.49									48			31		
8.0	15		120	28	20.1	0.59									49			30		
8.5	15		120	35	39.6	0.79									39			46		
9.0	15		119	28	29.5	0.64									42			42		
9.5	30		116	37	32.2	0.64									47			45		
10.0	30	186/96	117	28	27.1	0.58				7.31	26		505	156	44	52	8	43		0.56
10.5	45		117	30	25.7	0.55									51			42		
11.0	45		120	32	32.0	0.74									44			40		
11.5	60		126	34	32.4	0.79									48			37		
12.0	60	192/99	128	29	33.5	0.83				7.28	25		467	191	48	55	7	37		0.54
12.5	75		131	32	34.6	0.85									47			38		
13.0	75		134	37	34.2	0.87									49			36		
13.5	90		136	33	36.5	0.94									51			36		
14.0	90	196/102	132	35	37.5	0.99				7.25	25		409	245	54	59	5	35		0.53
14.5	105		144	39	40.1	1.08									51			34		
15.0	105	207/102	145	37	41.3	1.10				7.23	25		350	302	54	51	7	35		0.55
15.5	120		145	40	47.0	1.31									52			33		
16.0	120		152	40	48.3	1.39									52			32		
16.5	135		153	45	54.7	1.54									53			33		
17.0	135	210/102	154	46	56.1	1.53				7.20	25		284	365	52	64	12	34		0.56
17.5	Recovery		149	43	53.9	1.51									53			33		
18.0	Recovery		144	43	51.7	1.38									52			35		
18.5	Recovery		136	41	46.1	1.13									47			38		
19.0	Recovery	192/102	133	39	44.1	1.03				7.22	22		475		47	55		40		

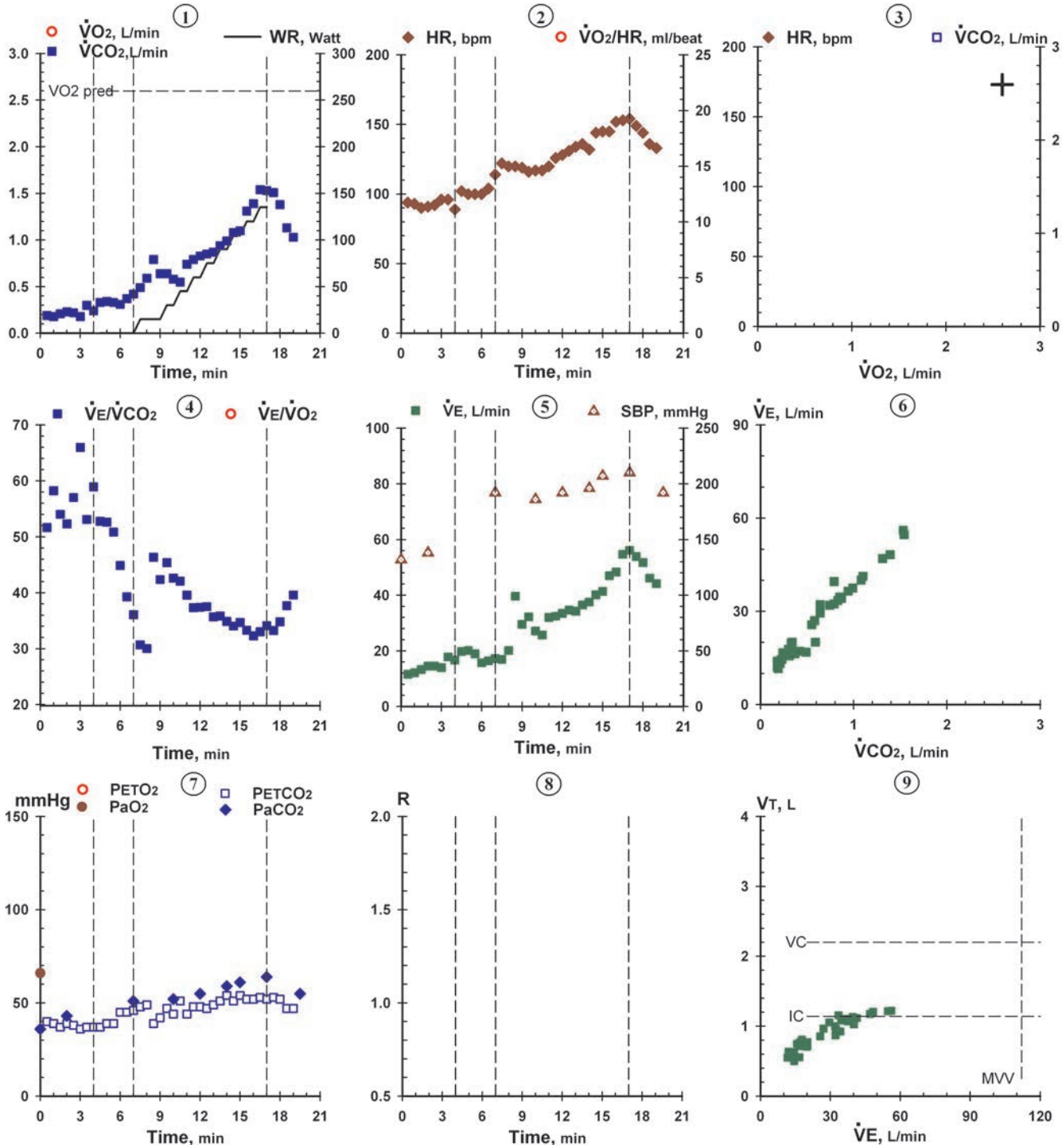

FIGURE 10.59.2. Oxygen breathing. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, the start of increasing work rate at 15 W per minute, and the start of recovery. Oxygen uptake data are not shown because of technical limitations for calculations with very high-inspired oxygen levels.

Case 60 Obesity Contributing to Ventilatory Limitation

CLINICAL FINDINGS

This 53-year-old former mechanic had retired because of medical disability 3 years previously due to vestibular neuronitis with symptoms of vertigo. He had no other complaints except for shortness of breath when bicycling uphill. He had 30 years of cigarette smoking and reported smoking a half a pack per day. Hypertension, diagnosed 14 years ago, was being treated with methyldopa. Chest radiographs were normal except for symmetric pleural thickening considered to represent extrapleural fat.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 15 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. Resting and exercise ECGs were normal. Resting carboxyhemoglobin was 7.4%. The patient stopped exercise, complaining of leg fatigue.

Table 10.60.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		53
Sex		Male
Height (cm)		171
Weight (kg)	74	104
Hematocrit (%)		51
VC (L)	4.15	4.00
IC (L)	2.77	3.64
TLC (L)	6.15	5.69
FEV_1 (L)	3.28	3.25
FEV_1/VC (%)	79	81
MVV (L/min)	140	126
D_{LCO} (mL/mm Hg/min)	28.8	29.8

INTERPRETATION

Comments

The patient's resting pulmonary function studies were normal, although the volumes were in the low-normal range and the ratio of expiratory reserve volume (ERV) to inspiratory capacity (IC) was low, consistent with obesity (Table 10.60.1). The patient was 30 kg overweight (see Table 10.60.1). The elevated carboxyhemoglobin suggested recent smoking. The ECG was normal.

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ and anaerobic threshold were within normal limits (Table 10.60.2). See Flowchart 2 (Fig. 8.2). The ECG, arterial blood gases, and O_2 pulse at peak $\dot{V}O_2$ were normal (branch point 2.1). The patient was overweight (branch point 2.2). In support of the conclusion that obesity was the cause of this patient's shortness of breath were the relatively high oxygen cost for unloaded cycling ($\dot{V}O_2$ = 0.9 L/min) and low breathing reserve at the maximum work rate (Fig. 10.60.1, panel 9 and Table 10.60.3). A low breathing reserve, indicating ventilatory limitation, can occur in patients with obstructive or interstitial lung disease due to increased ventilatory demand due to V:Q mismatch along with reduced ventilatory capacity; ventilatory limitation can also occur in highly conditioned individuals who attain high rates of $\dot{V}O_2$ and $\dot{V}CO_2$. In this case, however, pulmonary gas exchange was normal and the patient was not highly conditioned. Ventilatory requirements were relatively high at any given work rate because the associated metabolic rate was exaggerated by the effects of obesity. The patient's elevated carboxyhemoglobin might also have contributed to the low anaerobic threshold with earlier onset of excess CO_2 production. As a result of increased CO_2 production, the patient approached his MVV at a normal peak $\dot{V}O_2$ despite the absence of lung disease.

Conclusion

Obesity, carboxyhemoglobinemia, and detraining combined to produce an exaggerated degree of exercise lactic acidosis and excess CO_2 production (see Fig. 10.60.1, panel 1). The increased ventilation required to accommodate the high rate of CO_2 production, together with ventilatory limitation due to obesity, likely accounts for the exercise-induced dyspnea.

Table 10.60.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.48	2.45
Maximum heart rate (beats/min)	167	168
Maximum O_2 pulse (mL/beat)	14.9	15.6
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	10.4
AT (L/min)	>1.07	1.15
Blood pressure (mm Hg [rest, max])		160/90, 274/137
Maximum $\dot{V}E$ (L/min)		116
Exercise breathing reserve (L/min)	>15	10
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.4	29.9
PaO_2 (mm Hg [rest, max ex])		81, 85
$P(A-a)O_2$ (mm Hg [rest, max ex])		26, 37
$PaCO_2$ (mm Hg [rest, max ex])		37, 34
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		1, –7
VD/VT (rest, heavy ex)		0.31, 0.23
HCO_3^- (mEq/L [rest, 2-min recov])		24, 14

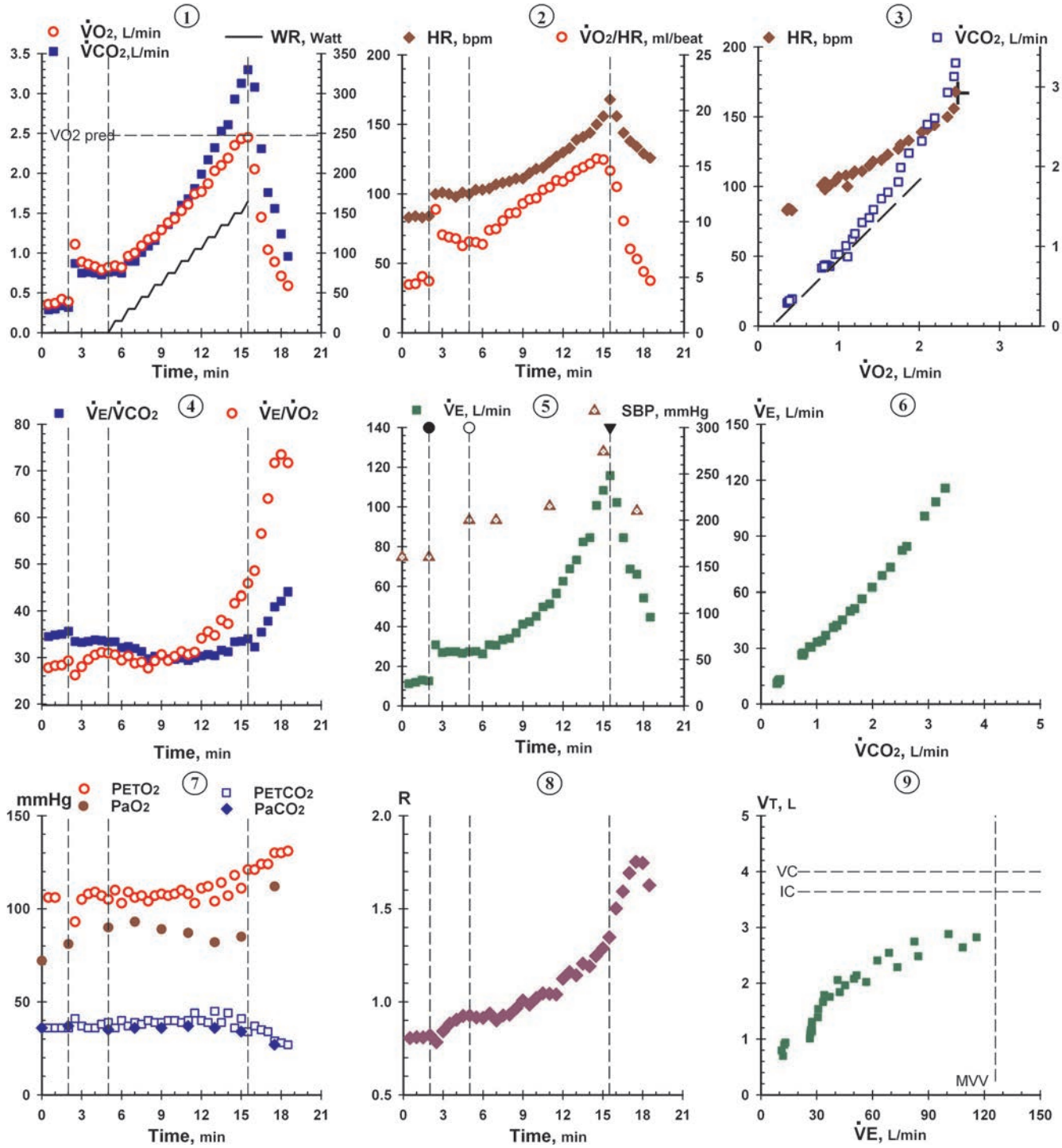

FIGURE 10.60.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.60.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
	Rest	160/100								7.44	24		72			36				
0.5	Rest		83	14	11.2	0.29	0.36	4.3	0.81			106			36			35	28	
1.0	Rest		84	17	11.9	0.30	0.37	4.4	0.81			106			36			35	28	
1.5	Rest		83	14	13.1	0.34	0.42	5.1	0.81			167			36			35	28	
2.0	Rest	160/90	84	14	12.6	0.32	0.39	4.6	0.82	7.43	24	168	81	26	36	37	1	36	29	0.31
2.5	Unloaded		100	20	30.8	0.87	1.11	11.1	0.78			93			41			33	26	
3.0	Unloaded		101	23	26.9	0.75	0.89	8.8	0.84			105			37			33	28	
3.5	Unloaded		100	22	27.3	0.76	0.86	8.6	0.88			108			36			33	30	
4.0	Unloaded		98	23	27.3	0.75	0.83	8.5	0.90			109			36			34	31	
4.5	Unloaded		101	24	26.6	0.73	0.79	7.8	0.92			107			38			34	31	
5.0	Unloaded	200/110	100	24	27.4	0.76	0.82	8.2	0.93	7.43	23	105	90	23	39	35	–4	33	31	0.24
5.5	15		103	21	27.5	0.77	0.84	8.2	0.92			110			36			33	31	
6.0	15		103	26	26.3	0.75	0.82	8.0	0.91			103			40			32	29	
6.5	30		104	20	30.8	0.90	0.96	9.2	0.94			109			37			32	30	
7.0	30	200/110	107	22	30.6	0.90	1.00	9.3	0.90	7.43	23	106	93	18	39	36	–3	32	29	0.23
7.5	45		108	20	33.3	1.01	1.09	10.1	0.93			107			38			31	29	
8.0	45		109	19	34.0	1.09	1.17	10.7	0.93			104			40			30	28	
8.5	60		111	21	36.9	1.16	1.20	10.8	0.97			107			39			30	29	
9.0	60		111	20	41.2	1.30	1.29	11.6	1.01	7.42	23	108	89	25	39	36	–3	30	31	0.20
9.5	75		115	23	42.4	1.36	1.38	12.0	0.99			107			40			30	29	
10.0	75		118	23	45.2	1.46	1.43	12.1	1.02			108			40			30	30	
10.5	90		119	24	49.9	1.60	1.53	12.9	1.05			110			39			30	31	
11.0	90	215/106	123	24	51.4	1.68	1.61	13.1	1.04	7.39	22	108	87	27	40	37	–3	29	31	0.20
11.5	105		127	28	56.6	1.81	1.74	13.7	1.04			103			44			30	31	
12.0	105		130	26	62.6	1.99	1.77	13.6	1.12			111			40			30	34	
12.5	120		133	27	68.8	2.17	1.87	14.1	1.16			112			39			31	36	
13.0	120		139	32	73.3	2.32	2.03	14.6	1.14	7.38	21	104	82	36	45	36	–9	30	35	0.20
13.5	135		141	30	82.4	2.53	2.10	14.9	1.20			114			39			32	38	
14.0	135		144	34	84.5	2.61	2.19	15.2	1.19			107			44			31	37	
14.5	150		150	35	100.8	2.93	2.35	15.7	1.25			118			36			33	42	
15.0	150	274/137	156	41	108.4	3.13	2.43	15.6	1.29	7.37	19	111	85	37	41	34	–7	34	43	0.23
15.5	165		168	41	115.8	3.30	2.45	14.6	1.35			121			34			34	46	
16.0	Recovery		156	33	102.3	3.08	2.05	13.1	1.50			121			37			32	49	
16.5	Recovery		144	30	84.5	2.31	1.45	10.1	1.59			124			35			35	57	
17.0	Recovery		138	25	68.7	1.76	1.04	7.5	1.69			124			34			38	64	
17.5	Recovery	210/100	134	27	66.1	1.56	0.89	6.6	1.75	7.32	14	130	112	20	29	27	–2	41	72	0.21
18.0	Recovery		129	26	54.4	1.24	0.71	5.5	1.75			130			28			42	74	
18.5	Recovery		126	28	44.7	0.96	0.59	4.7	1.63			131			27			44	72	

Case 61 Extrapulmonary Restriction: Ankylosing Spondylitis

CLINICAL FINDINGS

This 51-year-old airline employee had first developed symptoms of ankylosing spondylitis, primarily involving the neck and thoracic spine, approximately 6 years prior to evaluation. He was treated with nonsteroidal anti-inflammatory agents. He had stopped smoking more than 10 years previously. On the basis of apical pleural changes on chest radiographs, he had been treated empirically for tuberculosis several years previously, although the tuberculin skin test was negative. To maintain fitness, he had begun running approximately 3 miles a day. In the several months prior to testing, he felt as if he "could not get enough air" into his lungs and found himself taking gasping breaths. Physical examination revealed reduced neck movement and thoracic expansion. Chest radiograph revealed apical pleural thickening. The ECG was normal.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 20 W per minute to his symptom-limited maximum. He stopped exercise because of shortness of breath. Exercise ECGs were normal except for a single interpolated ventricular premature contraction.

INTERPRETATION

Comments

A spirometry indicated mild restrictive disease (Table 10.61.1). This was reflected primarily in a reduction in the inspiratory capacity, due to impaired expansion of the chest wall.

Analysis

In Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ and the anaerobic threshold were normal (Table 10.61.2). See Flowchart 2 (Fig. 8.2). The ECG and O_2 pulse at peak $\dot{V}O_2$ were normal (branch point 2.1). The subject was not obese (branch point 2.2). The normal $\dot{V}E/\dot{V}CO_2$ at the anaerobic threshold suggests that ventilation–perfusion matching was normal. The finding that tidal volume approximated inspiratory capacity (Fig. 10.61.1, panel 9 and Table 10.61.3) reflects the changes that would be expected from restrictive pulmonary or chest wall disease. Note that the MVV value identified in Figure 10.61.1 is the directly measured MVV. However, the MVV maneuver was performed at an unphysiologic breathing frequency of 80 per minute.

Table 10.61.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		51
Sex		Male
Height (cm)		178
Weight (kg)	80	79
Hematocrit (%)		39
VC (L)	4.62	3.61
IC (L)	3.08	2.60
FEV_1 (L)	3.67	2.76
FEV_1/VC (%)	79	76
MVV (L/min, direct)	151	132 at f = 80/min
MVV (L/min, indirect)	147	110

Table 10.61.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.52	2.54
Maximum heart rate (beats/min)	169	170
Maximum O_2 pulse (mL/beat)	14.9	14.9
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	9.4
AT (L/min)	>1.08	1.4
Blood pressure (mm Hg [rest, max])		126/86, 206/84
Maximum $\dot{V}E$ (L/min)		108
Exercise breathing reserve (L/min)	>15	2
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.9	24.3

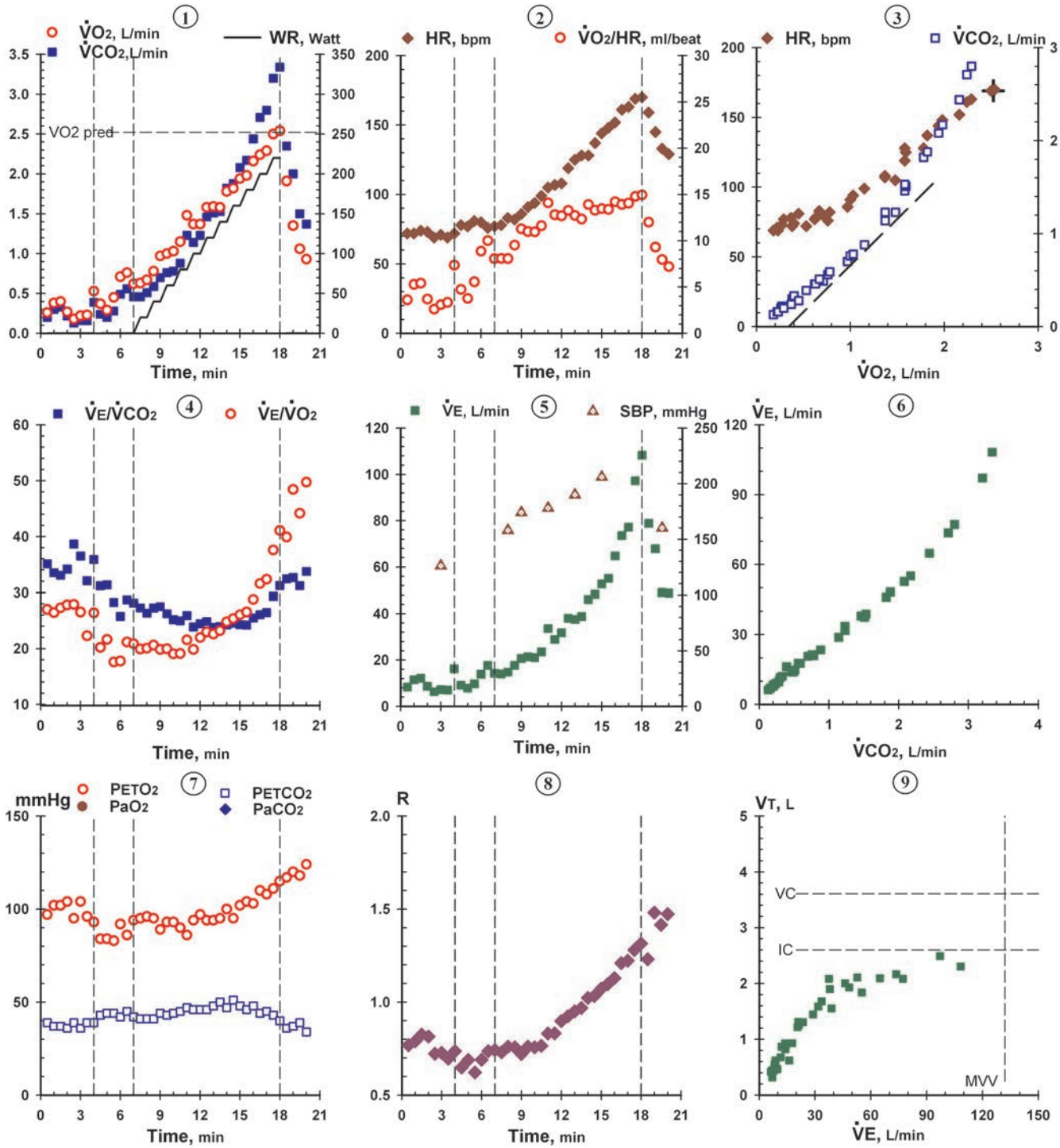

FIGURE 10.61.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

The indirect MVV (see Table 10.61.1) is a more reasonable estimate of his breathing capacity and approximated his peak exercise ventilation, indicating virtually no breathing reserve. This is reasonable evidence of ventilatory limitation.

Conclusion

The subject had exertional dyspnea and ventilatory limitation resulting from extrapulmonary restriction of the chest wall consequent to ankylosing spondylitis.

TABLE 10.61.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest		72	15	8.3	0.20	0.26	3.6	0.77			97			39			35	27	
0.5	Rest		72	17	11.5	0.30	0.38	5.3	0.79			102			37			34	26	
1.0	Rest		74	14	12.1	0.33	0.40	5.4	0.83			102			37			33	27	
1.5	Rest		73	14	8.7	0.22	0.27	3.7	0.81			104			36			34	28	
2.0	Rest		69	15	6.3	0.13	0.18	2.6	0.72			95			39			39	28	
2.5	Rest	126/86	71	16	7.2	0.16	0.22	3.1	0.73			104			36			37	27	
3.0	Rest		69	22	7.0	0.16	0.23	3.3	0.70			96			39			32	22	
3.5	Rest		72	26	16.2	0.39	0.53	7.4	0.74			93			39			36	26	
4.0	Unloaded		78	19	9.1	0.24	0.37	4.7	0.65			84			43			31	20	
4.5	Unloaded		77	18	7.8	0.20	0.29	3.8	0.69			84			44			31	22	
5.0	Unloaded		81	21	9.7	0.28	0.45	5.6	0.62			83			44			28	18	
5.5	Unloaded		80	15	13.9	0.49	0.71	8.9	0.69			92			42			26	18	
6.0	Unloaded		76	19	17.7	0.56	0.76	10.0	0.74			86			45			29	21	
6.5	Unloaded		77	16	14.3	0.46	0.62	8.1	0.74			94			42			28	21	
7.0	20		78	17	14.0	0.46	0.63	8.1	0.73			95			41			27	20	
7.5	20	158/86	83	16	14.8	0.51	0.67	8.1	0.76			96			41			26	20	
8.0	40		82	19	17.7	0.59	0.78	9.5	0.76			95			41			27	21	
8.5	40	174/84	86	17	20.7	0.70	0.97	11.3	0.72			89			44			28	20	
9.0	60		91	17	21.4	0.76	1.00	11.0	0.76			93			43			26	20	
9.5	60		94	16	21.0	0.78	1.03	11.0	0.76			93			44			25	19	
10.0	80		99	18	23.5	0.88	1.15	11.6	0.77			90			45			25	19	
10.5	80	178/78	105	20	33.6	1.23	1.48	14.1	0.83			86			47			26	22	
11.0	100		107	20	28.9	1.14	1.37	12.8	0.83			94			46			24	20	
11.5	100		108	20	31.8	1.23	1.37	12.7	0.90			97			46			24	22	
12.0	120		119	20	38.0	1.46	1.58	13.3	0.92			94			46			25	23	
12.5	120	190/86	125	18	37.5	1.51	1.59	12.7	0.95			94			48			24	23	
13.0	140		128	25	38.8	1.53	1.58	12.3	0.97			95			50			24	23	
13.5	140		128	23	46.1	1.82	1.78	13.9	1.02			100			47			24	25	
14.0	160		137	25	48.3	1.88	1.82	13.3	1.03			95			51			25	25	
14.5	160	206/84	144	25	52.7	2.08	1.94	13.5	1.07			102			48			24	26	
15.0	180		148	30	55.1	2.17	1.98	13.4	1.10			104			46			24	27	
15.5	180		152	31	64.8	2.44	2.16	14.2	1.13			103			48			25	29	
16.0	200		161	34	73.6	2.71	2.24	13.9	1.21			110			44			26	32	
16.5	200		163	37	77.2	2.80	2.29	14.0	1.22			108			45			26	32	
17.0	220		169	39	97.2	3.20	2.50	14.8	1.28			111			43			29	38	
17.5	220		170	47	108.3	3.34	2.54	14.9	1.31			115			40			31	41	
18.0	Recovery		159	32	78.9	2.35	1.91	12.0	1.23			117			36			32	40	
18.5	Recovery		145	30	67.9	2.00	1.35	9.3	1.48			120			37			33	48	
19.0	Recovery	160/78	133	27	49.1	1.50	1.06	8.0	1.42			118			39			31	44	
19.5	Recovery		129	30	48.8	1.37	0.93	7.2	1.47			124			34			34	50	

Case 62 Extrapulmonary Restriction: Scoliosis

CLINICAL FINDINGS

This 62-year-old attorney was referred for evaluation of suspected pulmonary vascular disease. He had scoliosis, which was progressive despite surgical treatment and bracing in childhood and was wary of medical or surgical procedures. He had shortness of breath and orthopnea since his 30s and used a wheelchair when he was outside his home. An echocardiogram had shown evidence of pulmonary hypertension, and he was advised to have right heart catheterization. He declined this in favor of an empiric trial of sildenafil, which he discontinued because of dizziness. Medical history included systemic hypertension. His medications included enalapril, hydrochlorothiazide, simvastatin, tiotropium, a steroid inhaler, and supplemental oxygen on an as-needed basis. The exam was notable for severe scoliosis of the thoracic spine with minimal breath sounds on the left side. Heart tones were regular and there was no edema, cyanosis, or clubbing. An ECG with a standard lead placement showed a sinus rhythm and voltage criteria for left ventricular hypertrophy.

EXERCISE FINDINGS

Exercise was performed on a cycle ergometer with the patient breathing room air. The patient cycled at 60 rpm without added load for a little less than 3 minutes (Fig. 10.62.1). He stopped with symptoms of shortness of breath, although he later said that he thought he could have continued further.

Table 10.62.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		62
Sex		Male
Height (cm)		163
Weight (kg)		83
VC (L)	3.74	0.83
IC (L)	2.85	0.77
FEV_1 (L)	2.81	0.63
FEV_1/VC (%)	78	76
MVV (L/min)	117	26

INTERPRETATION

Comments

Spirometry demonstrated severe restrictive lung mechanics without evidence of airflow obstruction (Table 10.62.1).

Analysis

Exercise performance was very limited and the patient stopped prior to completing the initial 3 minutes of unloaded pedaling, with a peak $\dot{V}O_2$ only about one-third of the predicted value (Table 10.62.2). It does not appear that the *AT* was reached (see Fig. 10.62.1, panel 3), and there was a large heart rate reserve. Although these findings indicate that this was likely a submaximal cardiovascular stress, there is considerable evidence that exercise was limited by ventilatory factors. Both the slow increase in $\dot{V}O_2$ at the start of exercise (see Fig. 10.62.1, panel 1) and low breathing reserve (see Fig. 10.62.1, panel 9) indicate that this exercise test likely represented a maximal or near-maximal effort. In addition to the low breathing reserve, pulse oximeter readings decreased from 92% at rest to 82% during exercise, and the patient stopped exercise with breathlessness. End-tidal P_{CO_2}, which was 50 mm Hg at rest, increased to 55 mm Hg during pedaling (see Fig. 10.62.1, panel 7), suggesting both chronic and

Table 10.62.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.94	0.63
Maximum heart rate (beats/min)	158	99
Maximum O_2 pulse (mL/beat)	12.3	6.4
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	NA
AT (L/min)	>0.9	NA
Blood pressure (mm Hg [rest, max])		155/84, 189/98
Maximum $\dot{V}E$ (L/min)		16
Exercise breathing reserve (L/min)	>15	10
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.8	27.2

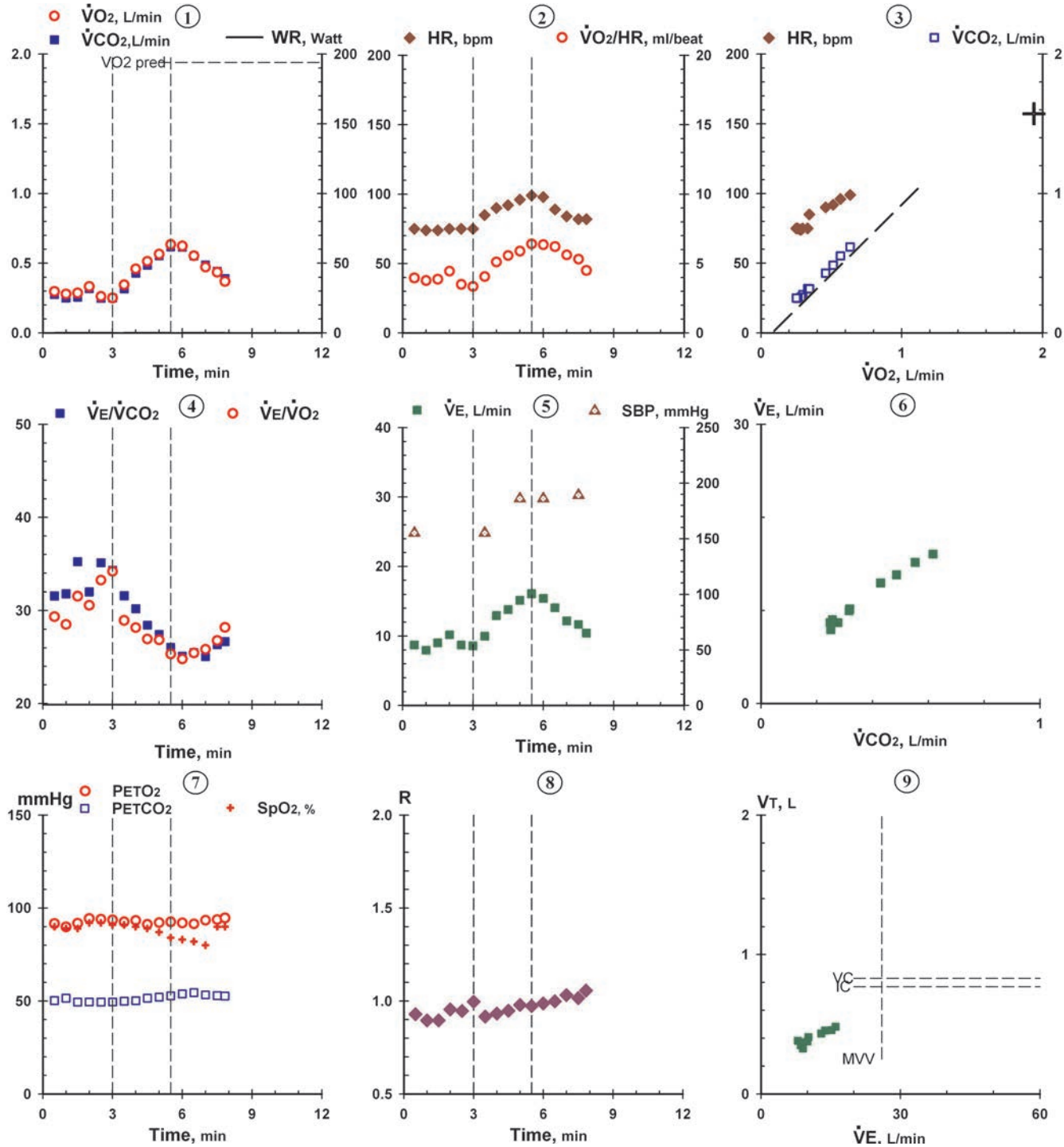

FIGURE 10.62.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling and start of recovery. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.62.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	155/84	75	24	8.7	0.28	0.30	4.0	0.93			92			50			32	29	
1.0	Rest		74	21	8.0	0.25	0.28	3.8	0.90			90			51			32	28	
1.5	Rest		74	28	9.0	0.26	0.29	3.9	0.90			92			49			35	32	
2.0	Rest		75	25	10.2	0.32	0.33	4.4	0.95			94			49			32	31	
2.5	Rest		75	24	8.7	0.25	0.26	3.5	0.95			94			49			35	33	
3.0	Unloaded		75	25	8.6	0.25	0.25	3.3	1.00			94			49			34	34	
3.5	Unloaded	155/84	85	27	10.0	0.32	0.35	4.1	0.92			93			50			32	29	
4.0	Unloaded		90	30	13.0	0.43	0.46	5.1	0.93			93			50			30	28	
4.5	Unloaded		92	30	13.8	0.49	0.51	5.6	0.95			91			52			28	27	
5.0	Unloaded	186/98	96	33	15.2	0.55	0.57	5.9	0.98			92			52			27	27	
5.5	Unloaded		99	33	16.1	0.62	0.63	6.4	0.97			93			53			26	25	
6.0	Recovery	186/98	98	32	15.4	0.62	0.62	6.4	0.99			92			54			25	25	
6.5	Recovery		89	29	14.1	0.55	0.55	6.2	1.00			91			55			25	25	
7.0	Recovery		84	24	12.2	0.49	0.47	5.6	1.03			93			53			25	26	
7.5	Recovery	189/95	82	25	11.7	0.44	0.44	5.3	1.02			94			53			26	27	
8.0	Recovery		82	21	10.4	0.39	0.37	4.5	1.06			95			53			27	28	

acute hypercapnia. Of note, $\dot{V}_E/\dot{V}_{CO_2}$ ratios fell into the normal range with exercise (Table 10.62.3). Although this is usually an indication that pulmonary V:Q matching is relatively normal, $\dot{V}_E$ may also be reduced relative to $\dot{V}_{CO_2}$ due to hypoventilation (CO_2 retention). The normal ventilatory equivalents recorded in this case do not necessarily exclude significant pulmonary V:Q mismatch. This patient's chronic hypoventilation spared him the need to increase $\dot{V}_E$ as much as normally required for any given increment in metabolic rate. Hypoventilation and ventilatory limitation during exercise likely contributed to arterial desaturation.

Conclusion

The patient had ventilatory limitation due to severely restricted lung mechanics. In addition, there was evidence of chronic hypoventilation, which is likely the basis for the echocardiographic findings of pulmonary arterial hypertension.

Case 63 McArdle Disease

CLINICAL FINDINGS

This 60-year-old elementary school teacher was referred for exercise testing by her pulmonologist for evaluation of long-standing exertional dyspnea of unclear cause. She recounted lifelong exercise intolerance to which she had adapted by taking a slow pace during prolonged activities, and avoiding strenuous activities or performing them in a "stop and go" mode. As a girl, she hid her exercise intolerance in gym classes by stopping to tie her shoes frequently. She was able to be a cheerleader because each cheer lasted less than 3 minutes, which was within her tolerance. As an adult, she could walk at a slow pace for extended distances but inclines or increases in speed caused the abrupt onset of dyspnea and fatigue, which then resolved quickly with rest. She denied muscle pain or dark urine. One of the patient's brothers had a similar degree of exercise limitation due to muscle pain and rhabdomyolysis, which had been diagnosed as McArdle disease (muscle phosphorylase deficiency). A third sibling was healthy with no exercise limitation. Because she had no pain or pigmenturia, the patient had never equated her exercise intolerance to her brother's and had not mentioned this family history to her treating physicians. Her medications included hydrochlorothiazide and lisinopril for hypertension. Her physical exam was normal.

EXERCISE FINDINGS

Exercise testing was performed initially on a cycle ergometer. The patient ended this test with shortness of breath and leg fatigue after only a few minutes of incremental work, but recovered promptly after several minutes of rest. In an attempt to obtain a longer test, testing was repeated with a treadmill walking protocol as a more familiar form of exercise. The patient initially walked at a self-selected pace of 1.7 mph and zero grade for 3 minutes, after which the grade was increased by 0.5% each minute. She was able to exercise for a little over 7 minutes on this test, which was stopped due to symptoms of leg fatigue and the patient's inability to keep up with the moving belt without handrail support.

Table 10.63.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		60
Sex		Female
Height (cm)		166
Weight (kg)		63
VC (L)	3.49	3.00
IC (L)	2.29	2.38
FEV_1 (L)	2.7	2.07
FEV_1/VC (%)	78	69
MVV (L/min)	95	86

Comments

Spirometry showed mild airflow obstruction (Table 10.63.1). Results of the two exercise tests were qualitatively similar, but the treadmill test contained more data and is presented in Figure 10.63.1 and Tables 10.63.2 and 10.63.3. Selected data from the cycle test are included in Table 10.63.2.

Analysis

There are several notable findings in this exercise test. The most unique is the relationship of $\dot{V}O_2$ and $\dot{V}CO_2$. The initial 3 minutes of walking at 1.7 mph was associated with an increase of $\dot{V}O_2$ to around 650 mL per minute (Fig. 10.63.1, panel 1) and with subsequent increase in grade, $\dot{V}O_2$ increased to a peak value that was

Table 10.63.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.48	0.91
Maximum heart rate (beats/min)	160	140
Maximum O_2 pulse (mL/beat)	9.3	7.6
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	NA
AT (L/min)	>0.79	Indeterminate
Blood pressure (mm Hg [rest, max ex])		124/85, 149/89
Maximum $\dot{V}E$ (L/min)		50
Exercise breathing reserve (L/min)	>15	36
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	29.4	36.2

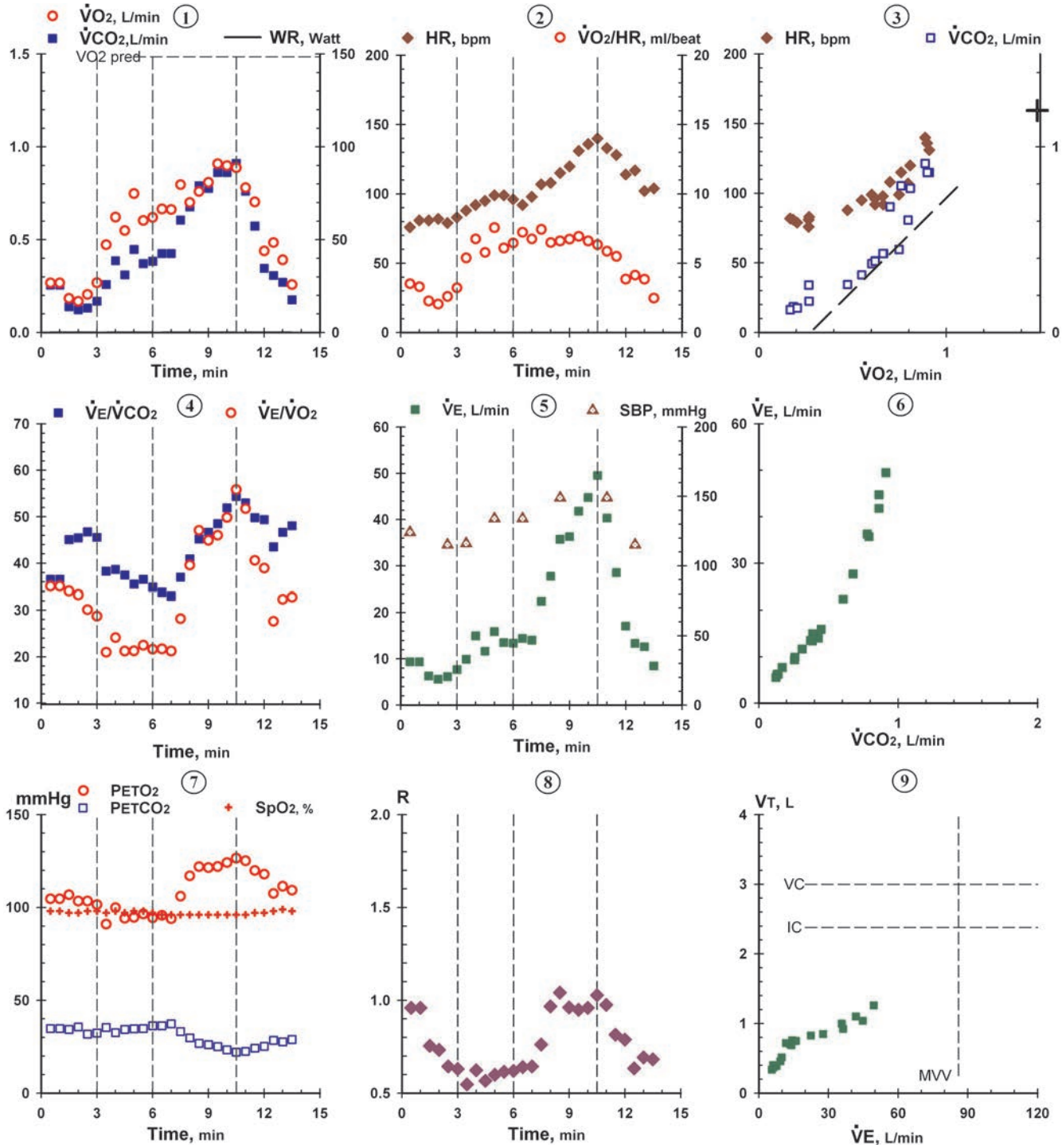

FIGURE 10.63.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of treadmill walking at a speed of 1.7 mph at zero grade, the start of increasing grade by 0.5% per minute, and the start of recovery. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.63.3

Air Breathing

Time (min)	Treadmill speed (mph)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0.5	Rest	124/85	76	20	9.4	0.26	0.27	3.5	0.96			105			35			37	35	
1.0	Rest		81	20	9.4	0.26	0.27	3.3	0.96			105			35			37	35	
1.5	Rest		81	17	6.3	0.14	0.18	2.3	0.76			107			34			45	34	
2.0	Rest		82	17	5.6	0.12	0.17	2.0	0.73			103			36			45	33	
2.5	Rest	115/77	79	15	6.2	0.13	0.21	2.6	0.64			103			32			47	30	
3.0	Rest		83	20	7.7	0.17	0.27	3.2	0.63			102			32			46	29	
3.5	0	116/76	88	19	9.9	0.26	0.47	5.4	0.55			91			35			38	21	
4.0	0		92	20	15.0	0.39	0.62	6.8	0.62			100			33			39	24	
4.5	0		95	16	11.7	0.31	0.55	5.8	0.57			94			34			37	21	
5.0	0	134/89	99	21	15.9	0.45	0.75	7.6	0.60			95			35			36	21	
5.5	0		99	19	13.6	0.37	0.60	6.1	0.62			97			35			37	22	
6.0	0		96	19	13.4	0.38	0.62	6.5	0.62			94			36			35	22	
6.5	0.5	134/89	92	19	14.4	0.43	0.67	7.2	0.64			96			36			34	22	
7.0	0.5		98	20	14.1	0.43	0.66	6.8	0.64			94			37			33	21	
7.5	1.0		107	27	22.4	0.61	0.80	7.4	0.76			106			33			37	28	
8.0	1.0		108	33	27.7	0.68	0.70	6.5	0.97			117			30			41	40	
8.5	1.5	149/89	115	36	35.7	0.79	0.76	6.6	1.04			122			27			45	47	
9.0	1.5		120	39	36.3	0.78	0.81	6.7	0.96			121			26			47	45	
9.5	2.0		131	38	41.8	0.86	0.91	6.9	0.95			122			25			49	46	
10.0	2.0		136	43	44.8	0.86	0.90	6.6	0.96			124			23			52	50	
10.5	2.5		140	39	49.5	0.91	0.89	6.3	1.03			127			22			54	56	
11.0	2.5		133	34	40.3	0.76	0.78	5.9	0.98			125			22			53	52	
11.5	Recovery		128	27	28.5	0.57	0.70	5.5	0.82			120			24			50	41	
12.0	Recovery		114	24	17.1	0.35	0.44	3.9	0.79			118			25			49	39	
12.5	Recovery	115/79	117	18	13.4	0.31	0.48	4.1	0.63			108			28			44	28	
13.0	Recovery		102	22	12.6	0.27	0.39	3.8	0.69			111			28			47	32	
13.5	Recovery		104	19	8.5	0.18	0.26	2.5	0.68			109			29			48	33	

around 60% of the predicted maximum value. Looking at panel 3 of Figure 10.63.1, there is a sharp break point in the V-slope at a $\dot{V}O_2$ of 0.80 L per minute, which $\dot{V}CO_2$ increases abruptly to 0.9 L per minute. Although this might appear to represent the anaerobic threshold, review of other plots show that this break point corresponds to the abrupt onset of hyperventilation (see Fig. 10.63.1, panel 7), which will be discussed below. The slope of the increase of $\dot{V}CO_2$ relative to $\dot{V}O_2$ prior to this break point was 0.7, suggesting that fat was the predominant substrate of the exercising muscle early in the test. (This was also true during the cycle test.) This is in contrast to the usual finding that during a short duration exercise test, the slope of $\dot{V}CO_2$ versus $\dot{V}O_2$ below the anaerobic threshold is around 1.0, reflecting carbohydrates as the preferred muscle substrate. Consistent with this, the patient's R value at rest during the 2 minutes prior to exercise was around 0.7, and it remained at this low level through the first 4 minutes of exercise (Table 10.63.3). At the end of the test, the R value decreased back to the resting level within 1 or 2 minutes. This, too, is unusual, as R normally increases in recovery.

As has been alluded to, at minute 7, when the treadmill grade was increased from 0.5% to 1.0%, there was an abrupt increase in ventilation with a marked decrease in $P_{ET}CO_2$, and increases in $P_{ET}O_2$, ventilatory equivalents, and R values (see Fig. 10.63.1, panels 5, 7, 4, and 8, respectively). The coincident and abrupt increase in $\dot{V}CO_2$ with very little increase in $\dot{V}O_2$ on the V-slope plot (see Fig. 10.63.1, panel 3) is atypical and supports the impression of acute hyperventilation. Soon after the onset of incremental work, there was a steepening of the heart rate relative to $\dot{V}O_2$ (see Fig. 10.63.1, panel 3) associated with an unchanging O_2 pulse (see Fig. 10.63.1, panel 2), which remained below the predicted maximal value. This implies either a low stroke volume at the start of exercise or an inability to widen $C(a - \bar{v})O_2$.

Many features of this test, including hyperventilation, are quite nonspecific. However, the shallow slope of $\dot{V}CO_2$ relative to $\dot{V}O_2$ and the failure to demonstrate an anaerobic threshold are uniquely suggestive of the condition pointed to by her family history. McArdle disease results from a deficiency of skeletal muscle phosphorylase, which prevents utilization of glycogen as a substrate. Exercising

muscle is thus dependent on fatty acids and circulating glucose as substrate for energy production. Because of the limited carbohydrate metabolism, little or no lactic acid is produced, which is consistent with the failure to identify a clear anaerobic threshold in this case. It has been suggested that the low peak $\dot{V}O_2$ in this condition results from a lack of local acidification of the muscle by lactic acid, resulting in failure to shift the oxyhemoglobin curve to the right to facilitate oxygen unloading (Bohr effect). This would limit $C(a - \bar{v})O_2$, which can account for the low O_2 pulse of this patient. Exercise hyperventilation, such as occurred in this case, is commonly described in McArdle disease, but the basis for it is not well-defined.

Conclusion

This patient's successful adaptation of exercise behavior to fit her capabilities delayed identification of a heritable muscle disease despite her family history. Her exercise responses reflected the metabolic consequences of this condition, though the occurrence of hyperventilation could easily distract one from the key findings.

Case 64 Myopathy with Exertional Rhabdomyolysis

CLINICAL FINDINGS

This 53-year-old man was referred for exercise testing to characterize his impairment due to an unspecified myopathy. He was normally active as a child and young adult. In his early 30s, he had consulted a rheumatologist for vague muscle symptoms but no specific diagnosis was made. At age 47, he had an episode of rhabdomyolysis complicated by acute renal failure after a day of river rafting, and over the next 5 years had several more documented episodes of rhabdomyolysis. Laboratory evaluation, including electrolytes, thyroid function tests, and autoimmune studies, had been normal, and electromyography showed nonspecific abnormalities. At the time of testing, he reported easy fatigability and delayed muscle soreness after modest levels of exertion. He worked part time as a nurse and did minimal exercise. Medical history included hypertension and prior back surgeries with residual chronic pain. He had undergone general anesthesia without adverse reactions. His family history was not contributory. His medications included metoprolol, lisinopril, and methadone. Examination demonstrated a normal body habitus without obvious skeletal muscle hypertrophy or wasting. The resting ECG was normal.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. After 3 minutes of rest, he pedaled at 60 rpm as work rate was increased by 20 W each minute. He stopped exercise due to shortness of breath and "burning" in his leg muscles. There were no significant ECG changes.

Table 10.64.1

Selected Demographic Data

Measurement	Predicted	Measured
Age (years)		53
Sex		Male
Height (cm)		181
Weight (kg)		86
Hematocrit (%)		43

Comments

Demographic data are shown in Table 10.64.1. Pulmonary function tests were not available. A muscle biopsy had been performed several years prior to this test and the patient was screened for the most commonly recognized enzyme deficiencies associated with rhabdomyolysis. The report indicated no specific structural abnormalities and normal staining for phosphorylase a and b, myoadenylate deaminase, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, and carnitine palmitoyltransferase. The basis of his myopathy, therefore, was not defined.

Analysis

The test appears to reflect good effort based on the high peak heart rate and end-exercise R value of close to 1.4, indicating substantial CO_2 from buffering of lactic acid (Fig. 10.64.1, panels 1 and 3). $\dot{V}O_2$ increased appropriately with work rate, but peak $\dot{V}O_2$ and *AT* were both low (Tables 10.64.2 and 10.64.3). The increase in heart rate was steep (see Fig. 10.64.1, panel 3) relative to $\dot{V}O_2$. The O_2 pulse (see Fig. 10.64.1, panel 2) increased during the first few minutes of exercise but failed to increase further and remained lower than the predicted maximum for the remainder of the test. These findings are consistent with either impairment in oxygen delivery (low stroke volume) or impaired oxygen extraction at the muscle level

Table 10.64.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.57	1.64
Maximum heart rate (beats/min)	167	150
Maximum O_2 pulse (mL/beat)	15.4	11.2
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.3	10.0
AT (L/min)	>1.16	0.89
Blood pressure (mm Hg [rest, max])		148/79, 198/89
Maximum $\dot{V}E$ (L/min)		63
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.0	24.9

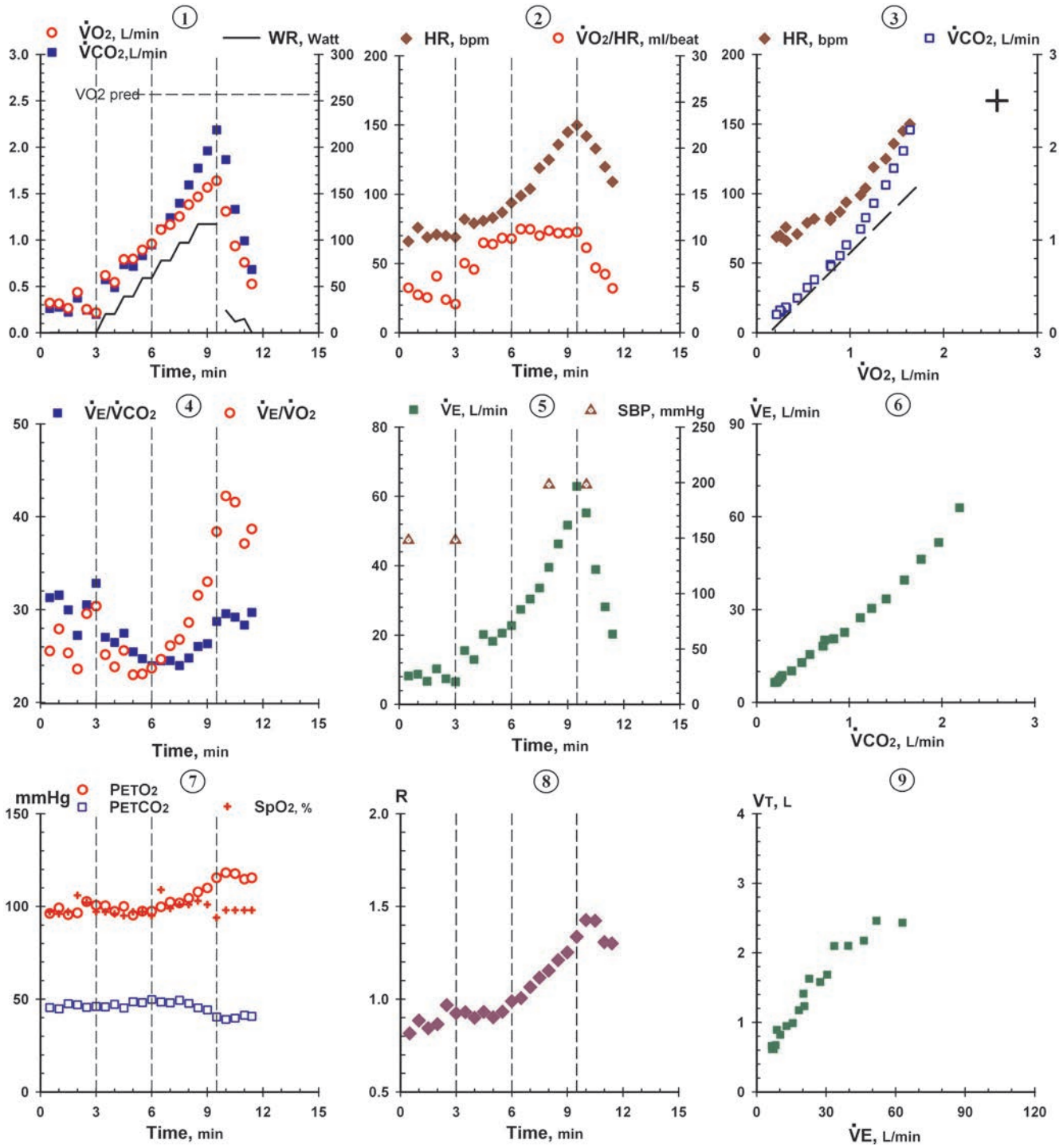

FIGURE 10.64.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of exercise with increasing work rate at 20 W per minute and the start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.64.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0																				
0.5	Rest	148/79	66	12	8.2	0.26	0.32	4.8	0.82			96			46			31	26	
1.0	Rest		76	10	8.7	0.28	0.31	4.1	0.88			99			45			32	28	
1.5	Rest		69	11	6.7	0.22	0.26	3.8	0.84			96			48			30	25	
2.0	Rest		71	12	10.2	0.38	0.43	6.1	0.87			97			47			27	24	
2.5	Rest		70	12	7.4	0.24	0.25	3.6	0.97			103			46			31	30	
3.0	Rest		69	10	6.5	0.20	0.21	3.1	0.93			101			46			33	30	
3.5	20		82	16	15.5	0.57	0.62	7.5	0.93			100			46			27	25	
4.0	20		79	14	12.9	0.49	0.54	6.9	0.90			97			47			26	24	
4.5	39		81	14	20.2	0.74	0.79	9.7	0.93			100			45			27	26	
5.0	39		83	16	18.3	0.72	0.80	9.6	0.90			95			49			25	23	
5.5	59		87	17	20.6	0.83	0.89	10.3	0.93			97			48			25	23	
6.0	59		94	14	22.7	0.95	0.96	10.2	0.99			97			50			24	24	
6.5	78		99	17	27.4	1.12	1.11	11.2	1.01			100			49			24	25	
7.0	78		104	18	30.4	1.24	1.17	11.2	1.07			102			48			25	26	
7.5	97		119	16	33.5	1.40	1.25	10.5	1.12			102			49			24	27	
8.0	97		125	19	39.5	1.59	1.38	11.0	1.15			104			48			25	29	
8.5	117	198/89	136	21	46.2	1.78	1.47	10.8	1.21			108			45			26	32	
9.0	117		145	21	51.7	1.96	1.57	10.8	1.25			110			44			26	33	
9.5	117		150	26	62.9	2.19	1.64	10.9	1.34			115			40			29	38	
10.0	Recovery		142	24	55.2	1.87	1.31	9.2	1.43			118			39			30	42	
10.5	Recovery	136/87	133	22	38.9	1.33	0.94	7.0	1.42			118			40			29	42	
11.0	Recovery		120	19	28.2	0.99	0.76	6.3	1.31			115			41			28	37	
11.4	Recovery		109	17	20.3	0.68	0.53	4.8	1.30			115			41			30	39	

[low $C(a - \bar{v})O_2$]. The latter explanation is most consistent with the clinical history. Reduction in the capacity for oxidation of substrate in the muscle with early lactic acidosis, as occurred in this patient, would be associated with an abnormally low $C(a - \bar{v})O_2$, reflecting failure to normally utilize and extract oxygen in the muscle. This would be consistent with a muscle myopathy involving mitochondria. A hyperdynamic circulatory response, suggested by the heart rate pattern, is characteristic of defects in skeletal muscle oxidation. The test showed typical gas exchange changes associated with lactic acidosis, making McArdle disease (myophosphorylase deficiency) unlikely.

Conclusion

Although a specific metabolic defect was not identified on this patient's muscle biopsy, the exercise findings are suggestive of a deficiency in mitochondrial oxidative metabolism.

Case 65 Congenital Mitochondrial Myopathy

CLINICAL FINDINGS

This 37-year-old man was referred for exercise testing to quantify the functional effects of his recently identified mitochondrial myopathy. A mitochondrial DNA mutation had been identified in his sister, leading to testing of the patient. The abnormality was a point mutation (base pair m3302 A>G), affecting a gene that codes for a tRNA, resulting in a defect in the function of complex I of the electron transport chain. The patient reported being normally active as a child and initially denied any functional impairment. However, he admitted to having diffuse muscle pain and stiffness, along with generalized fatigue, at the end of a day working as a busboy in a restaurant. On several occasions, this was severe enough to require assistance to stand and walk. He was characterized as having mild cognitive impairment but denied other features associated with mitochondrial mutation syndromes such as seizures, stroke, diabetes, or hearing or visual problems. An echocardiogram had shown left ventricular hypertrophy with normal systolic function. He was taking no medications. On exam, he was normally developed but had low muscle bulk. Heart and lung exams were unremarkable. The resting ECG showed findings consistent with left ventricular hypertrophy.

EXERCISE FINDINGS

Exercise testing was performed on a cycle ergometer beginning with 3 minutes of cycling at 60 rpm without added load, followed by a continuous increase in work rate by 15 W per minute. The patient had difficulty adjusting to breathing through the mouthpiece, and the test was interrupted briefly at the end of the unloaded cycling period to adjust the breathing apparatus. With some encouragement, he was able to complete the test and ended exercise with leg fatigue as his sole symptom. There were no significant ECG changes.

Comments

Pulmonary function testing showed moderate lung restriction without evidence of airflow obstruction. The DLCO was also mildly reduced (Table 10.65.1), but when indexed to alveolar volume, it was within normal limits.

Analysis

Although the patient initially had some difficulty with test procedures, he clearly exceeded his *AT* and reached an R of 1.2 and a heart rate of 156 bpm at end exercise, indicating that this test represents at least a near-maximal effort. There were no significant ECG changes with exercise. Peak $\dot{V}O_2$ and anaerobic threshold were both reduced (Table 10.65.2) and the $\Delta\dot{V}O_2/\Delta WR$ slope was lower than normal. Peak O_2 pulse was low and remained flat over the period of incremental work (Fig. 10.65.1, panel 2). Consistent with this, the heart rate increased steeply relative to $\dot{V}O_2$ (see Fig. 10.65.1, panel 3). These findings indicate impairment in oxygen delivery and/or utilization. Cardiac, as

Table 10.65.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		37
Sex		Male
Height (cm)		165
Weight (kg)		57
VC (L)	3.82	3.10
TLC (L)	6.26	4.57
FEV_1 (L)	3.17	2.96
FEV_1/VC (%)	82	95
MVV (L/min)	127	118
DLCO (mL/mm Hg/min)	25.5	15.8

Table 10.65.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.33	0.78
Maximum heart rate (beats/min)	183	156
Maximum O_2 pulse (mL/beat)	12.7	5.0
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	6.2
AT (L/min)	>1.02	0.60
Blood pressure (mm Hg [rest, max])		110/76, 172/108
Maximum $\dot{V}E$ (L/min)		32
Exercise breathing reserve (L/min)	>15	76
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.0	32.5

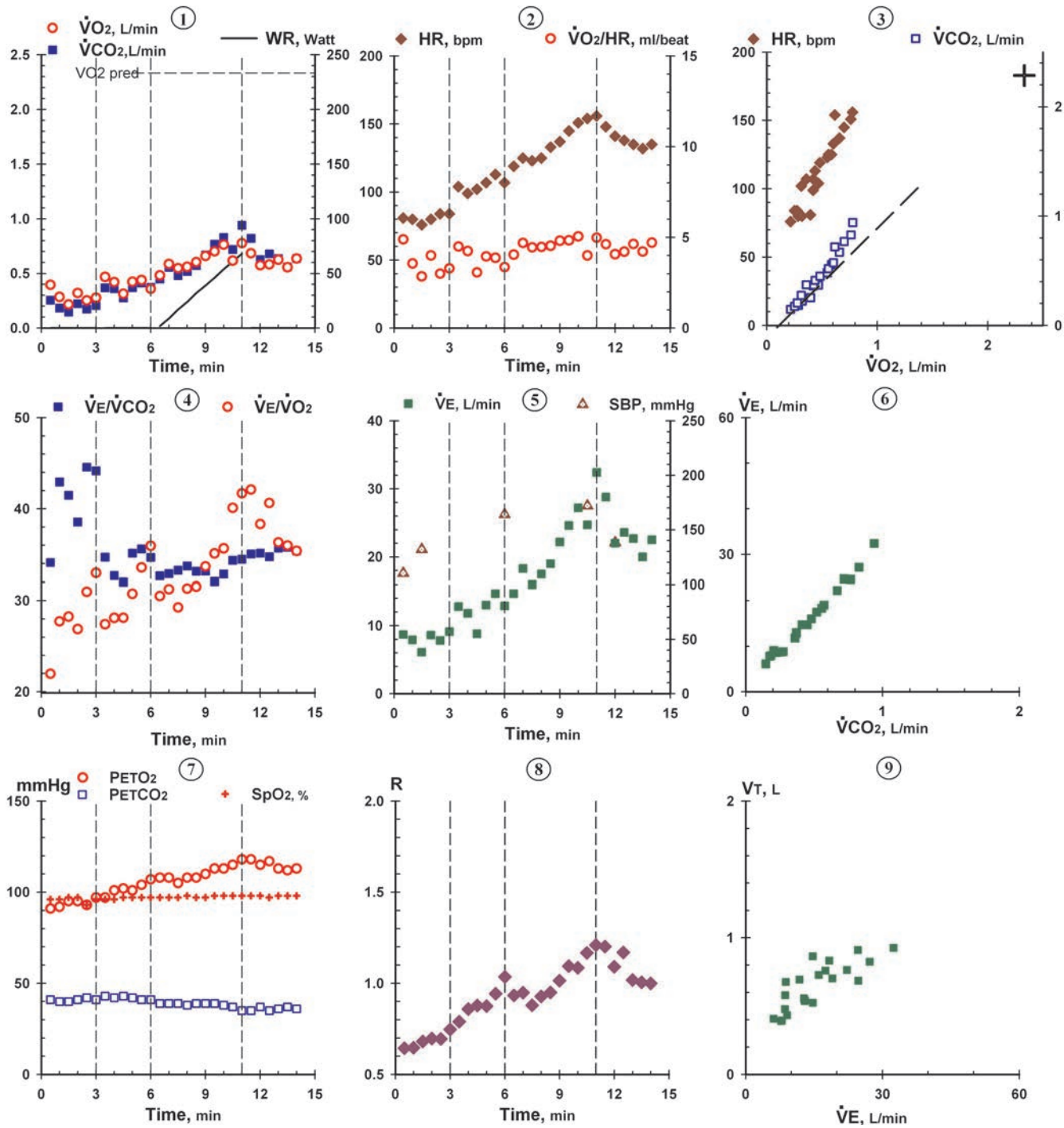

FIGURE 10.65.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.65.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	110/76	81	15	8.7	0.26	0.39	4.9	0.64			91			41			34	22	
1.0	Rest		80	20	7.9	0.18	0.28	3.6	0.65			92			40			43	28	
1.5	Rest	132/91	76	15	6.1	0.15	0.22	2.8	0.68			95			40			41	28	
2.0	Rest		80	18	8.6	0.22	0.32	4.0	0.70			95			41			39	27	
2.5	Rest		84	20	7.8	0.18	0.25	3.0	0.69			93			42			45	31	
3.0	Rest		84	21	9.1	0.21	0.28	3.3	0.75			97			41			44	33	
3.5	Unloaded		104	23	12.8	0.37	0.47	4.5	0.79			97			43			35	27	
4.0	Unloaded		99	17	11.8	0.36	0.42	4.2	0.86			101			42			33	28	
4.5	Unloaded		102	13	8.8	0.28	0.31	3.1	0.88			102			43			32	28	
5.0	Unloaded		107	24	13.0	0.37	0.42	3.9	0.87			101			42			35	31	
5.5	Unloaded		113	28	14.7	0.41	0.44	3.9	0.94			104			41			36	34	
6.0	Unloaded	164/98	107	24	12.9	0.37	0.36	3.4	1.04			107			41			35	36	
6.5	2		119	17	14.7	0.45	0.48	4.0	0.93			108			39			33	30	
7.0	9		125	22	18.3	0.56	0.59	4.7	0.95			108			39			33	31	
7.5	17		123	22	16.0	0.48	0.55	4.4	0.88			105			39			33	29	
8.0	24		125	23	17.5	0.52	0.56	4.5	0.93			108			38			34	31	
8.5	32		133	27	19.0	0.57	0.60	4.5	0.95			108			39			33	32	
9.0	39		137	29	22.2	0.67	0.66	4.8	1.02			110			39			33	34	
9.5	46		145	27	24.6	0.77	0.70	4.8	1.09			113			39			32	35	
10.0	54		151	33	27.2	0.83	0.76	5.0	1.09			113			38			33	36	
10.5	61	172/108	154	36	24.7	0.72	0.62	4.0	1.17			115			37			34	40	
11.0	68		156	35	32.4	0.94	0.78	5.0	1.21			118			35			34	42	
11.5	Recovery		148	37	28.8	0.82	0.68	4.6	1.20			118			35			35	42	
12.0	Recovery	138/89	141	35	22.0	0.63	0.57	4.1	1.09			115			37			35	38	
12.5	Recovery		138	29	23.6	0.68	0.58	4.2	1.17			117			35			35	41	
13.0	Recovery		135	32	22.7	0.64	0.62	4.6	1.02			113			36			36	36	
13.5	Recovery		132	31	20.0	0.56	0.56	4.2	1.01			112			37			36	36	
14.0	Recovery		135	31	22.5	0.64	0.64	4.7	1.00			113			36			35	35	

well as skeletal muscle involvement of his mitochondrial disorder, was suggested by the presence of left ventricular hypertrophy, but as there were no clinical or echocardiographic findings to suggest heart failure, it seemed likely that impairment in peripheral muscle oxygen utilization was the dominant cause of O_2 flow impairment. With respect to the ventilatory response to exercise, there was an adequate breathing reserve and no evidence of arterial desaturation. The ventilatory equivalents are at the upper limit of normal (Table 10.65.3 and Fig. 10.65.1), however, raising the possibility of pulmonary V:Q mismatch. This may be due to the patient's relatively shallow breathing pattern, which has the effect of preventing V_D/V_T from falling as much as normal.

Conclusion

This case is presented as an illustration of findings of abnormal oxygen uptake in a patient with a mitochondrial myopathy.

Case 66 Mitochondrial Myopathy

CLINICAL FINDINGS

This 52-year-old woman was referred for testing because of progressive exercise intolerance over many years. She had been athletic through young adulthood, but in her mid-30s, she began to experience the abrupt onset of severe fatigue and weakness with heavy exertion, especially swimming. At one time, she was suspected of having hypokalemic periodic paralysis (a defect in muscle potassium channels), but this diagnosis was excluded. Her activity tolerance progressively decreased, and at the time of referral, she reported fatigue, dyspnea, and weakness on ascending a flight of stairs or walking in a store. No family members had similar problems. An echocardiogram showed normal cardiac structure and function. Cardiac catheterization had shown normal coronary arteries. Her history was otherwise notable for several episodes of transient ischemic events or strokes in her 40s with minimal neurologic residua. She had a curative resection of a bronchoalveolar cell lung cancer and remote optic nerve tumor. Exam was notable only for a thin body habitus.

EXERCISE FINDINGS

Exercise was performed on a cycle ergometer. After cycling at 60 rpm for 3 minutes without added load, work rate was increased continuously by 10 W per minute to her maximal tolerance. She ended exercise with symptoms of leg weakness and an inability to maintain the pedaling cadence, along with generalized weakness and shortness of breath. She required assistance in dismounting the ergometer and 10 minutes of seated recovery before she felt able to stand independently.

Comment

The spirometry results were normal (Table 10.66.1).

Analysis

The peak $\dot{V}O_2$ was very low and the $\Delta\dot{V}O_2/\Delta WR$ was markedly reduced (Table 10.66.2 and Fig. 10.66.1, panel 1). The *AT* from the V-slope plot (see Fig. 10.66.1, panel 3) was also reduced. The progressive rise in R throughout exercise (Table 10.66.3) is consistent with early onset of lactic acidosis. The O_2 pulse increased initially at the start of exercise but failed to increase further over the next 6 minutes of exercise (see Fig. 10.66.1, panel 2). The low peak O_2 pulse implies either low stroke volume or low $C(a-\bar{v})O_2$. $\dot{V}E/\dot{V}CO_2$ was high and $PETCO_2$ was low throughout the test, consistent with respiratory compensation for lactic acidosis, primary hyperventilation, or high pulmonary V:Q. Based on the V slope in panel 3, it appears that she exceeded the anaerobic threshold during the initial period of unloaded cycling, so the high $\dot{V}E/\dot{V}CO_2$ is most likely due

Table 10.66.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		52
Sex		Female
Height (cm)		178
Weight (kg)		64
VC (L)	4.31	4.27
IC (L)	2.59	2.02
FEV_1 (L)	3.39	2.98
FEV_1/VC (%)	80	70
MVV (L/min)	109	102

Table 10.66.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.54	0.62
Maximum heart rate (beats/min)	168	108
Maximum O_2 pulse (mL/beat)	9.1	6.0
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	2.0
AT (L/min)	> 0.78	0.49
Blood pressure (mm Hg [rest, max])		103/63, 139/95
Maximum $\dot{V}E$ (L/min)		37
Exercise breathing reserve (L/min)	>15	65
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.1	40.6

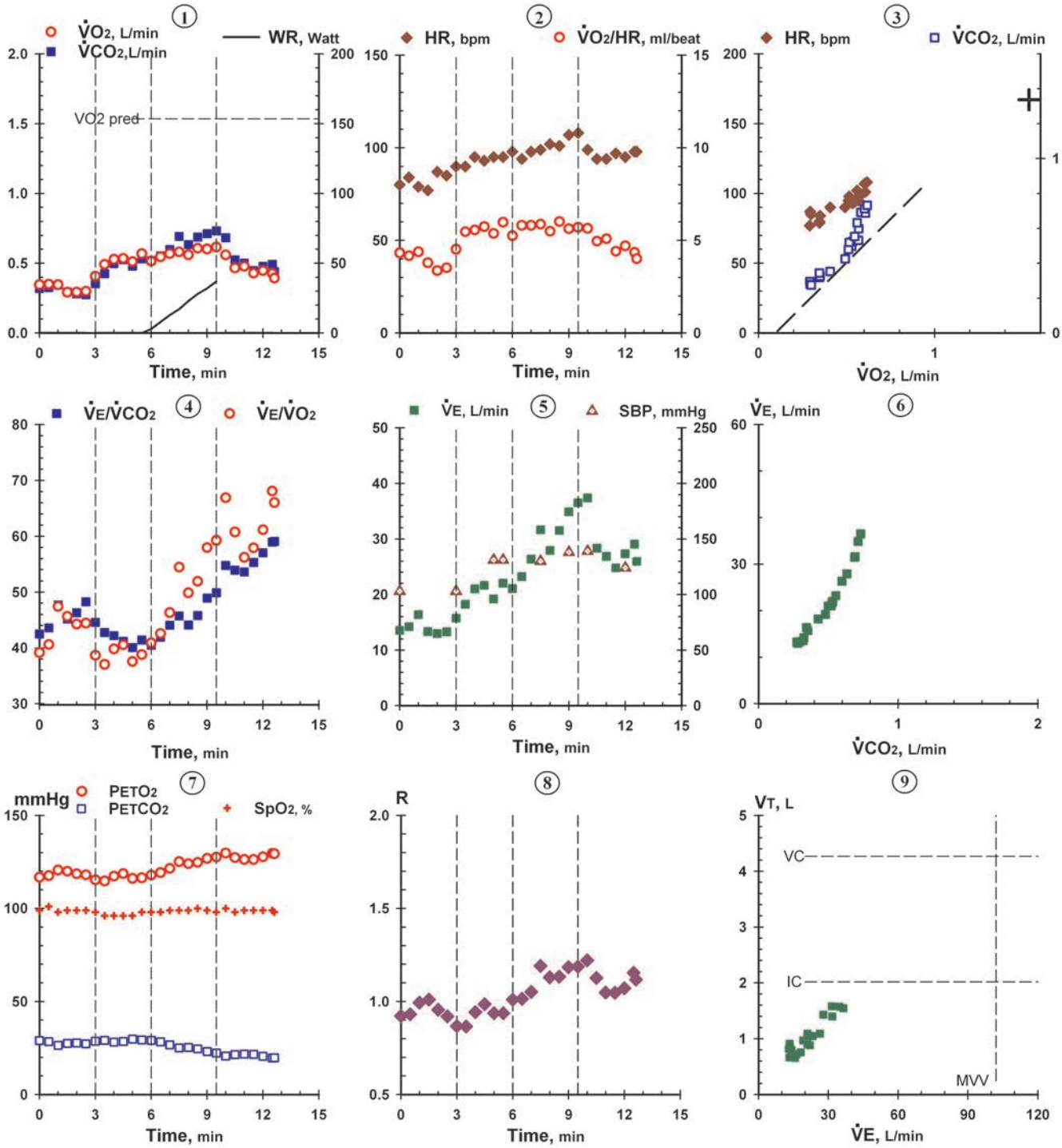

FIGURE 10.66.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.66.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0.5	Rest	103/63	80	16	13.6	0.32	0.35	4.3	0.92			117			29			42	39	
1.0	Rest		84	18	14.2	0.33	0.35	4.2	0.93			118			28			44	41	
1.5	Rest		79	23	16.4	0.34	0.35	4.4	0.99			121			26			48	47	
2.0	Rest		77	15	13.3	0.30	0.29	3.8	1.01			120			28			45	46	
2.5	Rest		87	16	13.0	0.28	0.29	3.4	0.96			119			28			46	44	
3.0	Rest		85	20	13.3	0.28	0.30	3.5	0.92			118			27			48	44	
3.5	Unloaded	103/63	90	24	15.7	0.35	0.41	4.5	0.87			115			29			45	39	
4.0	Unloaded		90	24	18.2	0.43	0.49	5.5	0.87			115			29			43	37	
4.5	Unloaded		95	23	21.0	0.50	0.53	5.6	0.94			117			28			42	40	
5.0	Unloaded		93	21	21.7	0.53	0.53	5.7	0.99			119			28			41	41	
5.5	Unloaded	131/60	95	20	19.2	0.48	0.51	5.4	0.94			116			30			40	38	
6.0	Unloaded		95	25	22.0	0.53	0.57	6.0	0.94			116			29			41	39	
6.5	3	131/80	98	19	21.1	0.52	0.52	5.3	1.01			118			29			41	41	
7.0	8		94	22	23.2	0.55	0.55	5.8	1.01			119			28			42	43	
7.5	13		98	24	26.4	0.60	0.57	5.8	1.05			122			27			44	46	
8.0	17		99	23	31.6	0.69	0.58	5.9	1.19			125			25			46	54	
8.5	23	130/85	102	20	27.9	0.63	0.56	5.5	1.13			124			25			44	50	
9.0	28		101	20	31.5	0.69	0.61	6.0	1.13			125			25			46	52	
9.5	32		107	22	34.9	0.71	0.60	5.6	1.18			127			23			49	58	
10.0	37	138/95	108	24	36.5	0.73	0.62	5.7	1.19			128			22			50	59	
10.5	Recovery	139/78	99	28	37.4	0.68	0.56	5.6	1.22			130			21			55	67	
11.0	Recovery		94	26	28.3	0.53	0.47	5.0	1.13			127			22			54	61	
11.5	Recovery		94	25	26.9	0.50	0.48	5.1	1.05			126			22			54	56	
12.0	Recovery		97	25	24.8	0.45	0.43	4.4	1.05			126			22			55	58	
12.5	Recovery	124/74	95	28	27.3	0.48	0.45	4.7	1.07			128			21			57	61	
13.0	Recovery		98	25	29.1	0.49	0.43	4.4	1.15			130			20			59	68	

to early onset of lactic acidosis. Furthermore, the abnormalities of O_2 pulse and reduced $\Delta\dot{V}O_2/\Delta WR$ were striking and indicative of severe abnormalities in O_2 delivery and/or muscle O_2 extraction. Given these findings, the history of weakness, and lack of evidence for a cardiovascular disorder, impaired skeletal muscle oxygen utilization was suspected. Evaluation for a muscle disorder was thus recommended and a muscle biopsy was subsequently performed at another facility. The findings were interpreted as indicative of a mitochondrial myopathy. The specific metabolic defect was not reported, but the patient's history of prior neurologic events suggested a variant of the MELAS (mitochondrial encephalopathy with myopathy, lactic acidosis, and stroke-like episodes) syndrome.

Conclusion

This was a challenging test to interpret, but the exercise findings and clinical history provided sufficient evidence to recommend a workup for a muscle oxidative disorder. Impairment of oxygen utilization by the muscle results in inadequate ATP regeneration to meet the increased demands of exercise, early onset of lactic acidosis, and low O_2 pulse due to failure of the $C(a - \bar{v})O_2$ to increase.

Case 67 Mixed Disorder: Chronic Bronchitis and Obesity

CLINICAL FINDINGS

This 69-year-old former shipyard worker was referred for exercise testing as part of an evaluation for occupational lung disease. He had noted dyspnea on exertion for 16 years, more recently associated with cough, sputum production, and wheezing. He had been exposed to asbestos and had a 15 pack-year history of cigarette smoking. He had been treated with bronchodilators and intermittent antibiotics for the past decade. Physical examination revealed obesity, bilaterally decreased breath sounds, and scattered expiratory wheezes. There was no evidence on examination for cardiovascular disease. Chest radiographs revealed moderate pleural thickening bilaterally and scattered parenchymal calcifications compatible with old granulomatous disease. The resting ECG showed left atrial enlargement and left ventricular hypertrophy.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 10 W per minute to his symptom-limited maximum. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercising, complaining of shortness of breath and chest tightness. There were no ST-segment changes or arrhythmia.

Table 10.67.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		69
Sex		Male
Height (cm)		166
Weight (kg)	70	98
Hematocrit (%)		45
VC (L)	3.31	2.91 (2.15[a])
IC (L)	2.21	2.35 (1.89[a])
TLC (L)	5.38	7.32
FEV_1 (L)	2.55	1.47 (1.30[a])
FEV_1/VC (%)	77	51 (60[a])
MVV (L/min)	112	56 (44[a])
DLCO (mL/mm Hg/min)	22.6	26.0

[a]On day of exercise study.

INTERPRETATION

Comments

Respiratory function studies demonstrate a moderate obstructive defect (Table 10.67.1). The ECG had findings of left ventricular hypertrophy and left atrial enlargement.

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ was low and anaerobic threshold was normal (Table 10.67.2). Proceeding to Flowchart 3 (Fig. 8.3), the breathing reserve was low (branch point 3.1), suggesting that lung disease accounted for this patient's reduced exercise performance. Supporting

Table 10.67.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.93	1.50
Maximum heart rate (beats/min)	151	125
Maximum O_2 pulse (mL/beat)	12.8	12.0
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	10.4
AT (L/min)	>0.87	1.35
Blood pressure (mm Hg [rest, max])		142/72, 234/99
Maximum $\dot{V}E$ (L/min)		55
Exercise breathing reserve (L/min)	>15	1
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	29.3	34.3
PaO_2 (mm Hg [rest, max ex])		73, 92
$P(A-a)O_2$ (mm Hg [rest, max ex])		32, 17
$PaCO_2$ (mm Hg [rest, max ex])		40, 39
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		6, 1
VD/VT (rest, heavy ex)		0.40, 0.35
HCO_3^- (mEq/L [rest,2-min recov])		26, 22

Table 10.67.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0	Rest	142/72								7.40	26		75			43				
0.5	Rest		78	24	12.4	0.27	0.35	4.5	0.77			103			36			38	30	
1.0	Rest		76	18	10.7	0.27	0.36	4.7	0.75			100			39			34	25	
1.5	Rest		79	24	11.4	0.23	0.30	3.8	0.77			100			38			41	31	
2.0	Rest	156/81	77	21	12.8	0.27	0.31	4.0	0.87	7.42	25	110	73	32	34	40	6	41	36	0.41
2.5	Rest		79	21	13.3	0.30	0.35	4.4	0.86			109			34			38	33	
3.0	Rest		80	22	12.9	0.24	0.28	3.5	0.86			110			34			46	39	
3.5	Unloaded		90	36	18.0	0.29	0.38	4.2	0.76			107			34			52	39	
4.0	Unloaded		98	50	28.0	0.53	0.66	6.7	0.80			108			34			45	36	
4.5	Unloaded		98	56	29.5	0.57	0.65	6.6	0.88			101			40			43	38	
5.0	Unloaded		101	43	31.8	0.79	0.89	8.8	0.89			99			42			36	32	
5.5	Unloaded		104	49	29.1	0.69	0.77	7.4	0.90			107			38			36	32	
6.0	Unloaded	198/93	105	47	34.6	0.76	0.85	8.1	0.89	7.40	26	106	82	22	39	42	3	40	36	0.43
6.5	10		102	55	41.2	0.90	0.96	9.4	0.94			110			36			41	38	
7.0	10		103	53	37.6	0.85	0.93	9.0	0.91			107			38			39	36	
7.5	20		105	58	46.3	0.98	0.99	9.4	0.99			114			34			42	42	
8.0	20	204/87	107	47	34.5	0.82	0.91	8.5	0.90	7.37	26	106	84	17	40	45	5	37	34	0.43
8.5	30		108	40	36.6	0.94	1.05	9.7	0.90			104			40			35	32	
9.0	30		109	50	39.8	0.95	1.05	9.6	0.90			105			39			37	34	
9.5	40		109	45	40.1	1.02	1.16	10.6	0.88			106			38			36	31	
10.0	40	207/87	110	46	42.2	1.11	1.28	11.6	0.87	7.38	24	106	80	23	38	42	4	34	30	0.37
10.5	50		113	47	42.1	1.09	1.23	10.9	0.89			105			39			35	31	
11.0	50		114	44	38.7	1.02	1.16	10.2	0.88			103			41			34	30	
11.5	60		117	45	47.1	1.26	1.39	11.9	0.91			107			39			34	31	
12.0	60	219/90	120	54	48.3	1.24	1.34	11.2	0.93	7.38	23	107	87	22	39	39	0	35	33	0.34
12.5	70		124	49	53.0	1.38	1.45	11.7	0.95			108			39			35	34	
13.0	70	234/99	125	50	55.0	1.43	1.50	12.0	0.95	7.37	32	110	92	17	38	39	1	35	34	0.35
13.5	Recovery		128	59	51.3	1.50	1.51	11.8	0.99			109			38			31	31	
14.0	Recovery		117	41	47.1	1.30	1.30	11.1	1.00			112			37			34	34	
14.5	Recovery		117	52	48.5	1.20	1.22	10.4	0.98			112			36			37	36	
15.0	Recovery		110	51	45.1	0.98	0.94	8.5	1.04			113			36			42	43	
15.5	Recovery	204/84	107	42	31.0	0.61	0.56	5.2	1.09	7.37	22	115	95	19	36	39	3	45	49	0.45

this is the finding that the indices of ventilation–perfusion matching [V_D/V_T, $P(A-a)O_2$, and $P(a-ET)CO_2$] were abnormal (Table 10.67.3) and the heart rate reserve was high.

The actual maximum work rate performed by the patient is quite low, despite only a mild reduction in peak $\dot{V}O_2$, because the patient had a relatively high oxygen cost for unloaded cycling ($\dot{V}O_2$ = 0.85 L/min) (see Fig. 10.67.1, panel 1). This is attributable to his obesity (added metabolic cost of moving his legs). The fall in $P(A-a)O_2$ and rise in PaO_2 when transitioning from rest to exercise suggest that the resting hypoxemia in this patient was attributable to obesity-related basilar microatelectasis that resolves with the increased ventilation accompanying exercise.

The elevated dead space fraction of the tidal volume (V_D/V_T) and high metabolic cost of exercise caused by obesity, combined with mechanical limitation to breathing imposed by obstructive lung disease, all contributed to the patient reaching exercise limitation at a low level of work.

Conclusion

Exertional dyspnea and ventilatory limitation is attributable to the combined effects of elevated ventilatory requirements of V:Q mismatch, elevated metabolic requirements of obesity, and reduced ventilatory capacity due to moderate obstructive lung disease.

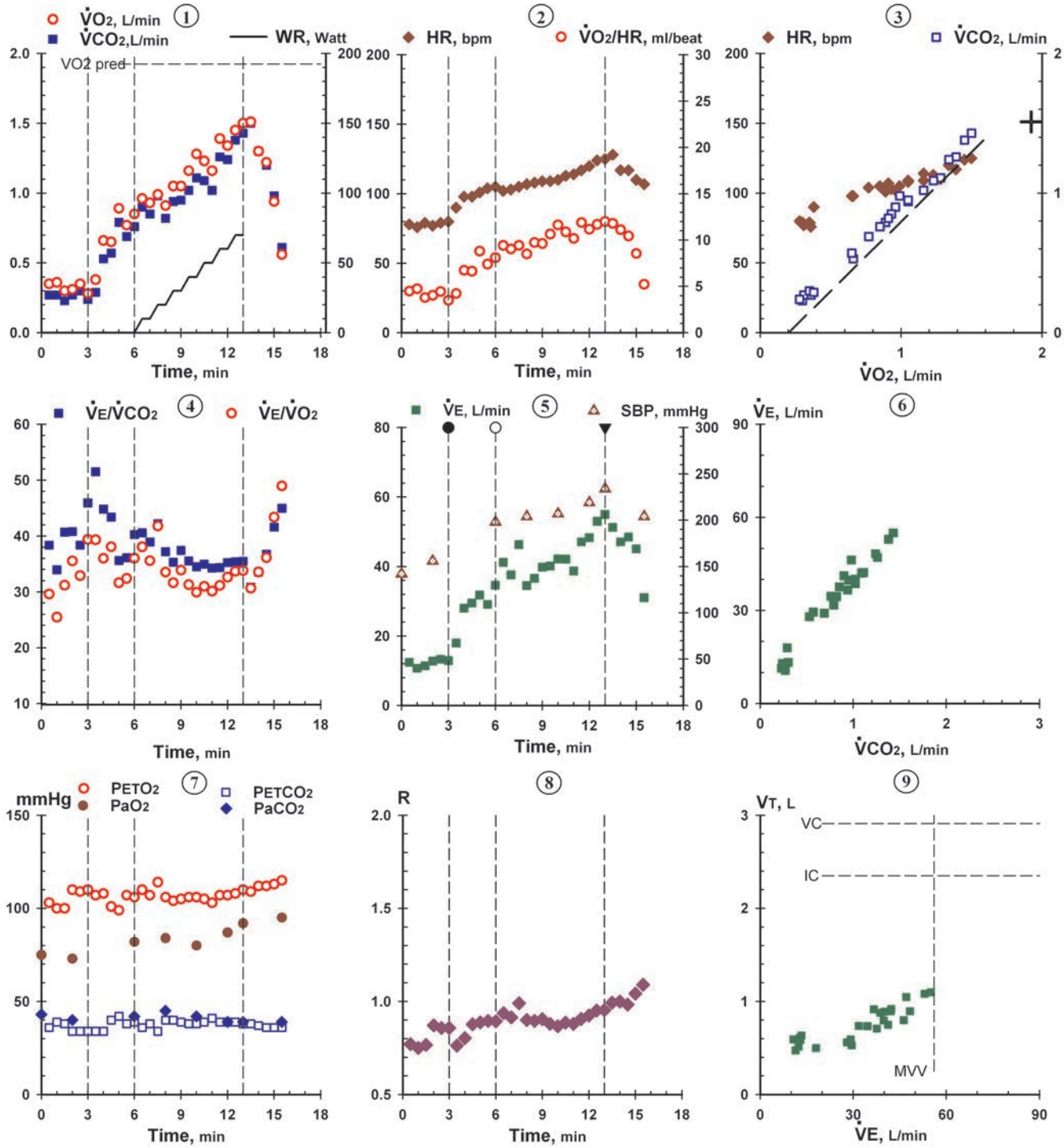

FIGURE 10.67.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 68 Mixed Disorder: Peripheral Arterial Disease, Anemia, Carboxyhemoglobinemia, and Cardiac Dysfunction

CLINICAL FINDINGS

This 54-year-old bartender was referred for preoperative study to evaluate his exercise capacity. He had smoked at least 60 pack-years but denied cardiac or respiratory symptoms. He reported calf pain after walking one block and occasionally also at rest. Lower extremity angiography had shown obstructive arterial disease in the left iliac and superficial femoral arteries. He was anemic (hematocrit = 34), with occult blood in the stool.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 15 W per minute to his symptom-limited maximum. Blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. Resting and exercise ECGs were normal. He stopped exercise because of severe leg pain, which was more prominent on the left.

Table 10.68.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		54
Sex		Male
Height (cm)		168
Weight (kg)	72	60
Hematocrit (%)		34
VC (L)	3.94	3.84
IC (L)	2.63	3.64
TLC (L)	5.86	7.16
FEV_1 (L)	3.12	3.07
FEV_1/VC (%)	79	80
MVV (L/min)	136	110
D_{LCO} (mL/mm Hg/min)	23.0	22.9

INTERPRETATION

Comments

The resting respiratory function is normal, including the diffusing capacity (Table 10.68.1). Carboxyhemoglobin was 5.6% on an arterial blood sample prior to exercise.

Analysis

The patient had a history of claudication and ended exercise with this symptom, consistent with his known peripheral arterial disease. Referring to the end of Flowchart 1 (Fig. 8.1), the category of peripheral arterial disease is characterized by several findings demonstrated in this case including leg pain, hypertension, mildly elevated heart rate reserve, and shallow $\Delta\dot{V}O_2/\Delta WR$ (Table 10.68.2).

Table 10.68.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.90	0.82
Maximum heart rate (beats/min)	161	141
Maximum O_2 pulse (mL/beat)	11.8	5.8
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	6.2
AT (L/min)	>0.84	0.7
Blood pressure (mm Hg [rest, max])		168/72, 255/114
Maximum $\dot{V}E$ (L/min)		60
Exercise breathing reserve (L/min)	<15	50
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.1	44.8
PaO_2 (mm Hg [rest, max ex])		94, 117
$P(A-a)O_2$ (mm Hg [rest, max ex])		20, 11
$PaCO_2$ (mm Hg [rest, max ex])		31, 26
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		3, 2
V_D/V_T (rest, heavy ex)		0.45, 0.38
HCO_3^- (mEq/L [rest, 2-min recov])		20, 16

Table 10.68.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0	Rest	168/72								7.43	20		90			31				
0.5	Rest		93	18	12.0	0.20	0.24	2.6	0.83			116			27			52	44	
1.0	Rest		94	15	14.0	0.25	0.29	3.1	0.86			117			28			51	44	
1.5	Rest		92	16	14.3	0.19	0.23	2.5	0.83			116			28			68	56	
2.0	Rest	168/72	95	14	11.7	0.19	0.23	2.4	0.83	7.42	20	116	94	20	28	31	3	55	46	0.45
2.5	Rest		93	16	12.6	0.22	0.29	3.1	0.76			113			29			51	39	
3.0	Rest		92	16	11.1	0.19	0.23	2.5	0.83			115			29			51	42	
3.5	Unloaded		100	19	15.7	0.27	0.32	3.2	0.84			117			28			52	44	
4.0	Unloaded		108	20	17.9	0.31	0.35	3.2	0.89			119			27			52	46	
4.5	Unloaded		109	20	19.1	0.34	0.39	3.6	0.87			118			27			51	45	
5.0	Unloaded		110	20	20.5	0.38	0.43	3.9	0.88			117			28			49	44	
5.5	Unloaded		110	22	22.5	0.45	0.50	4.5	0.90			118			28			46	41	
6.0	Unloaded	231/93	111	21	22.3	0.46	0.52	4.7	0.88	7.43	20	117	97	20	28	30	2	45	39	0.33
6.5	15		114	22	25.2	0.54	0.59	5.2	0.92			118			28			43	40	
7.0	15		116	24	27.1	0.57	0.61	5.3	0.93			120			27			44	41	
7.5	30		118	24	26.8	0.56	0.59	5.0	0.95			119			28			44	42	
8.0	30	245/102	121	24	32.3	0.68	0.69	5.7	0.99	7.43	19	121	106	15	27	29	2	45	44	0.31
8.5	45		127	28	37.4	0.74	0.69	5.4	1.07			124			25			47	51	
9.0	45		128	31	40.1	0.78	0.72	5.6	1.08			124			26			48	52	
9.5	60		134	36	48.6	0.86	0.72	5.4	1.19			129			23			53	63	
10.0	60	255/114	141	38	59.7	1.02	0.82	5.8	1.24	7.44	17	128	117	11	24	26	2	55	69	0.38
10.5	Recovery		123	30	43.9	0.83	0.72	5.9	1.15			137			25			50	57	
11.0	Recovery		113	25	38.6	0.74	0.61	5.4	1.21			127			25			49	60	
11.5	Recovery		110	28	35.9	0.66	0.52	4.7	1.27			128			25			51	64	
12.0	Recovery	258/102	107	26	31.7	0.59	0.46	4.3	1.28	7.39	16	127	117	11	26	27	1	50	64	0.34

However, this patient also demonstrated high $\dot{V}E/\dot{V}CO_2$ values, which are not an intrinsic characteristic of peripheral arterial disease (branch point 4.3). $\dot{V}E/\dot{V}CO_2$ may be elevated due to either hyperventilation or to ventilation–perfusion mismatch characterized as high VD/VT. From the normal resting and exercise R value (~0.8), acute hyperventilation was not the cause in this case. Furthermore, although blood gas values indicated chronic respiratory alkalosis (Table 10.68.3), this did not fully account for the elevated $\dot{V}E/\dot{V}CO_2$, as the calculated VD/VT was also high (see Tables 10.68.2 and 10.68.3). The abnormally high $\dot{V}E/\dot{V}CO_2$ and VD/VT suggests ventilation–perfusion mismatch secondary to lung disease and/or left ventricular heart failure. Because the pulmonary function tests were normal, the high VD/VT should not be attributed to lung disease. This leads to the conclusion that the patient's physiologic abnormalities included left ventricular failure (Fig. 10.68.1, panels 1, 2, 3, 4, and 6). His impairment was augmented by an approximate 35% reduction in arterial O_2 content resulting from anemia and carboxyhemoglobinemia despite a normal PaO_2. These several factors combined to impair O_2 flow to the exercising muscle as manifest in the steep heart rate versus $\dot{V}O_2$ relation (Fig. 10.68.1, panel 3), early anaerobic threshold, and low O_2 pulse.

Conclusion

Although the patient stopped exercise due to the local symptoms of ischemic peripheral arterial disease, the gas exchange analyses identified impairment of central hemodynamics, which, together with anemia, carboxyhemoglobinemia, and the peripheral vascular lesions, combined to limit the capacity for oxygen flow to the exercising muscle.

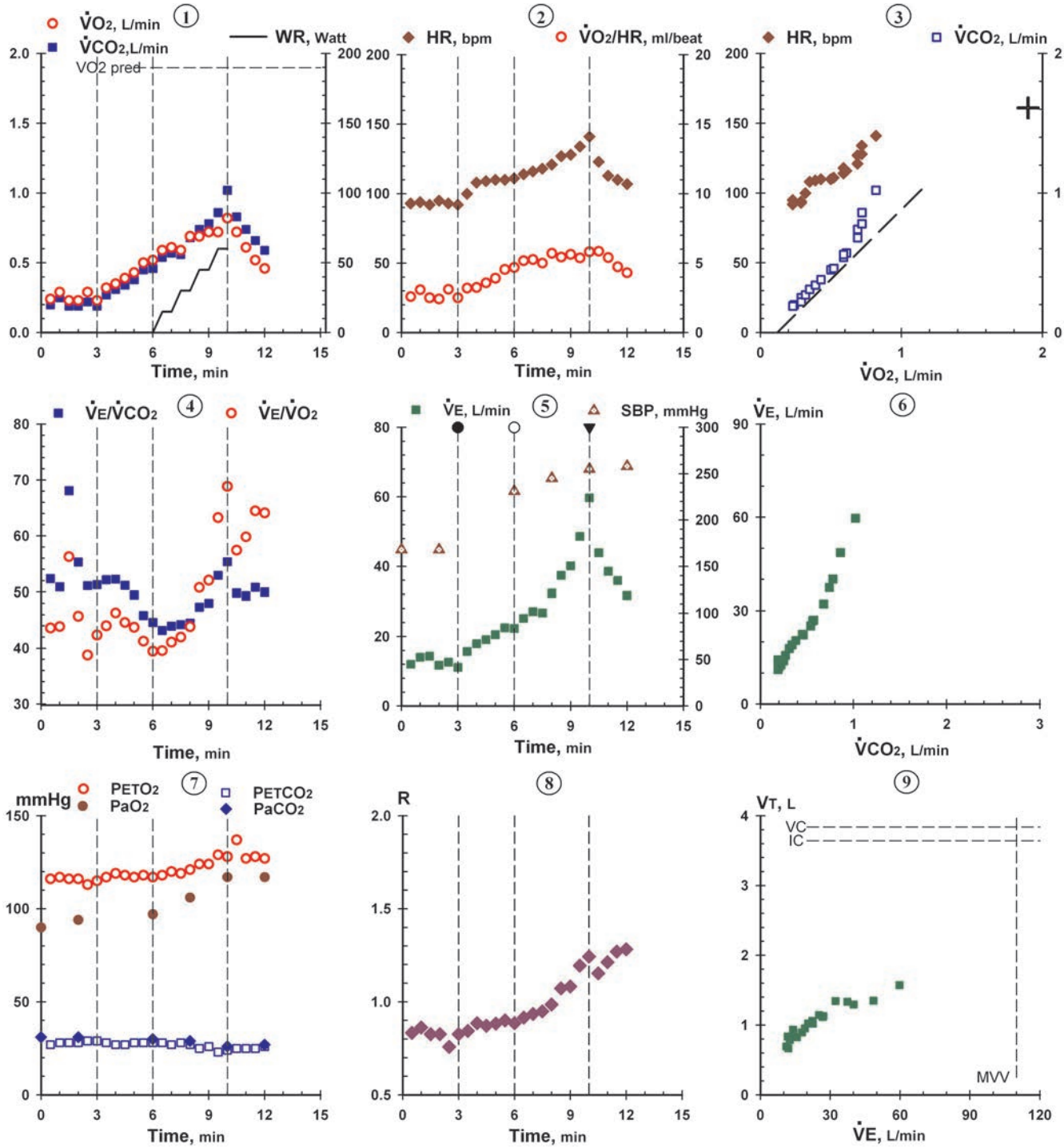

FIGURE 10.68.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 69 Mixed Disorder: Mild Interstitial Lung Disease, Obstructive Airway Disease, and Myocardial Ischemia

CLINICAL FINDINGS

This 54-year-old man was referred for cardiopulmonary exercise testing because of his work exposure to asbestos of 15 years. He was a former smoker with a 30-pack-year history of cigarette use. He denied dyspnea, cough, chest pain, weight change, or ankle edema. He got little exercise and felt numbness in his legs after 20 minutes of walking. He had borderline hypertension and dyslipidemia. There were crackles at the left lung base, and a chest roentgenogram showed linear interstitial changes in that area. Heart sounds and the resting ECG were normal.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 15 W per minute to tolerance. Heart rate and rhythm were continuously monitored; 12-lead ECGs were obtained during rest, exercise, and recovery. Blood pressure was measured with a sphygmomanometer, and arterial oxygen saturation was estimated with a pulse oximeter. The patient appeared to give a good effort and stopped exercise because of leg fatigue; he denied chest pain or dyspnea during or after the study. Significant ST-segment depression in leads II, III, aVF, and V_3 to V_6 was noted beginning at the 120-W work rate, with a maximum of 2.5 mm depression at end of exercise. The ST-segment abnormalities resolved after 9 minutes of recovery. No ectopy was present. Saturation as estimated by oximetry remained normal.

INTERPRETATION

Comments

Resting studies showed a mild ventilatory defect, which is at least in part due to airflow obstruction; the DLCO was normal (Table 10.69.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ was mildly decreased, but the anaerobic threshold was normal (Table 10.69.2). Proceeding next to Flowchart 3 (Fig. 8.3), the high breathing reserve (branch point 3.1) and abnormal exercise ECG (branch point 3.3) lead to the diagnosis of myocardial ischemia, although the patient had no chest pain or distress. The $\Delta\dot{V}O_2/\Delta WR$ was within normal limits, but the plateau in the O_2 pulse for the last 4 minutes of exercise at a level below the predicted maximum (Fig. 10.69.1, panel 2) suggests that either both stroke volume

Table 10.69.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		54
Sex		Male
Height (cm)		191
Weight (kg)	90	98
Hematocrit (%)		47
VC (L)	5.36	4.79
IC (L)	3.58	3.78
FEV_1 (L)	4.25	3.05
FEV_1/VC (%)	79	64
MVV (L/min)	164	126
DLCO (mL/mm Hg/min)	29.5	27.7

Table 10.69.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.81	2.09
Maximum heart rate (beats/min)	166	142
Maximum O_2 pulse (mL/beat)	16.9	14.8
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.9
AT (L/min)	>1.21	1.4
Blood pressure (mm Hg [rest, max])		154/90, 198/78
Maximum $\dot{V}E$ (L/min)		72
Exercise breathing reserve (L/min)	>15	54
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.8	28.4

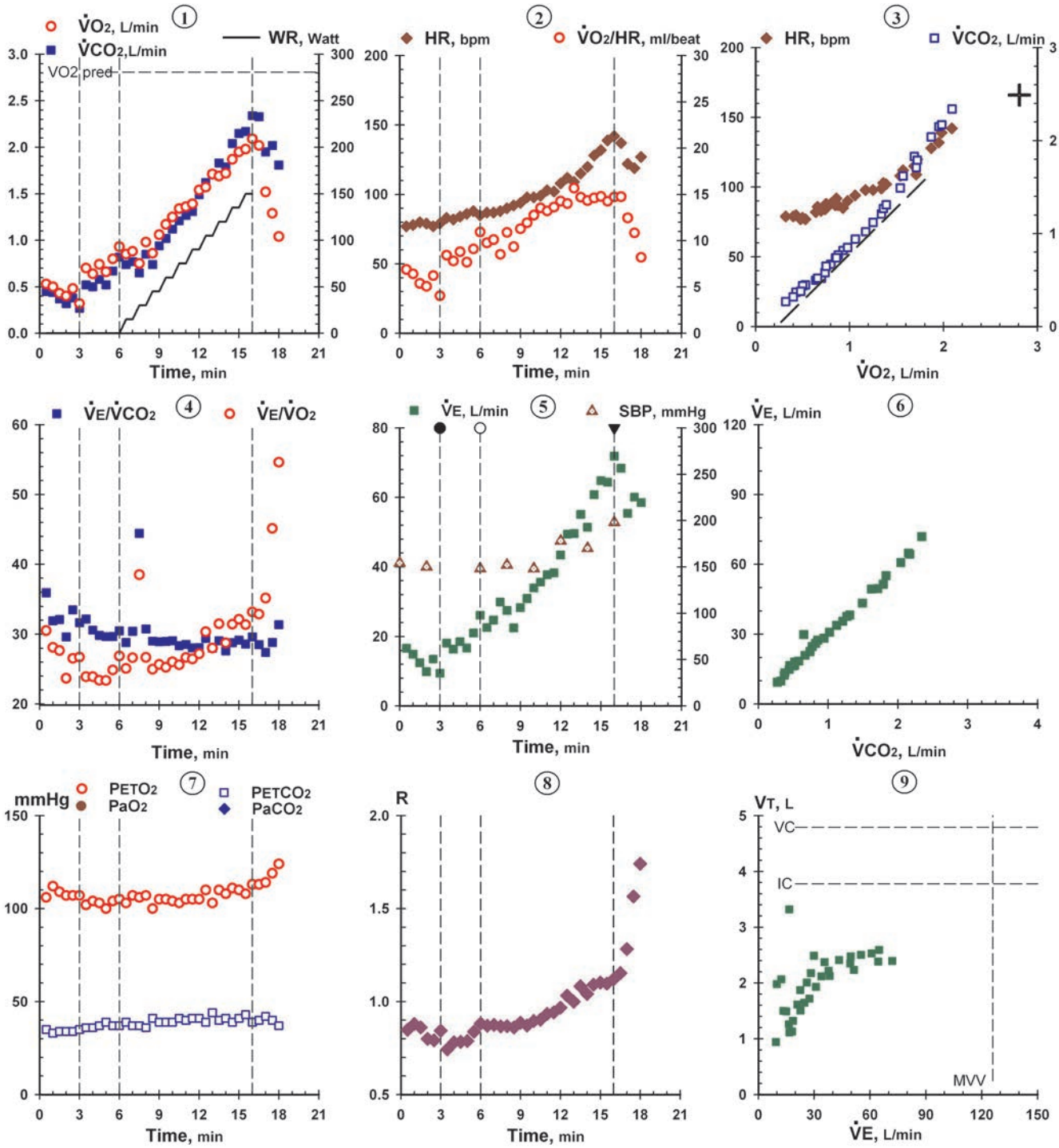

FIGURE 10.69.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.69.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	154/90																		
0.5	Rest		77	5	16.6	0.45	0.53	6.9	0.85			106			35			36	31	
1.0	Rest		78	10	14.9	0.44	0.50	6.4	0.88			112			33			32	28	
1.5	Rest		80	6	12.4	0.37	0.43	5.4	0.86			109			34			32	28	
2.0	Rest	150/96	79	5	9.9	0.32	0.40	5.1	0.80			107			34			30	24	
2.5	Rest		77	9	13.5	0.38	0.48	6.2	0.79			107			34			34	27	
3.0	Rest		79	10	9.4	0.27	0.32	4.1	0.84			107			35			32	27	
3.5	Unloaded		83	16	18.1	0.52	0.70	8.4	0.74			102			36			32	24	
4.0	Unloaded		82	13	16.4	0.50	0.64	7.8	0.78			104			36			31	24	
4.5	Unloaded		84	14	18.5	0.58	0.74	8.8	0.78			103			37			30	23	
5.0	Unloaded		86	15	16.7	0.52	0.66	7.7	0.79			100			39			30	23	
5.5	Unloaded		88	13	21.0	0.67	0.80	9.1	0.84			104			37			30	25	
6.0	Unloaded	148/88	85	13	26.1	0.82	0.93	10.9	0.88			105			37			30	27	
6.5	15		87	15	22.6	0.74	0.85	9.8	0.87			103			39			29	25	
7.0	15		87	15	24.7	0.77	0.88	10.1	0.88			107			37			30	27	
7.5	30		88	12	19.9	0.65	0.75	8.5	0.87			106			37			29	25	
8.0	30	152/90	90	16	27.5	0.85	0.98	10.9	0.87			107			36			31	27	
8.5	45		92	12	22.5	0.74	0.86	9.3	0.86			100			41			29	25	
9.0	45		94	13	28.3	0.94	1.06	11.3	0.89			105			39			29	26	
9.5	60		98	16	30.9	1.02	1.17	11.9	0.87			105			39			29	25	
10.0	60	148/84	98	16	33.9	1.12	1.25	12.8	0.90			104			39			29	26	
10.5	75		99	15	35.6	1.21	1.34	13.5	0.90			103			41			28	26	
11.0	75		103	17	37.7	1.27	1.36	13.2	0.93			105			40			29	27	
11.5	90		102	18	38.3	1.31	1.39	13.6	0.94			105			41			28	26	
12.0	90	178/86	108	18	43.4	1.49	1.54	14.3	0.97			105			41			28	27	
12.5	105		112	21	49.4	1.62	1.57	14.0	1.03			110			39			29	30	
13.0	105		109	20	49.6	1.71	1.71	15.7	1.00			103			44			28	28	
13.5	120		115	22	55.1	1.83	1.69	14.7	1.08			110			40			29	31	
14.0	120	170/88	120	23	51.4	1.79	1.72	14.3	1.04			108			41			28	29	
14.5	135		128	24	60.8	2.04	1.87	14.6	1.09			111			39			29	31	
15.0	135		132	25	64.8	2.15	1.95	14.8	1.10			110			41			29	32	
15.5	150		139	27	64.4	2.17	1.98	14.2	1.10			108			43			29	31	
16.0	150	198/78	142	30	71.9	2.34	2.09	14.7	1.12			113			39			30	33	
16.5	Recovery		137	23	68.4	2.33	2.02	14.7	1.15			113			40			29	33	
17.0	Recovery		122	23	55.4	1.95	1.52	12.5	1.28			114			42			27	35	
17.5	Recovery		119	22	60.1	2.02	1.29	10.8	1.57			119			40			29	45	
18.0	Recovery		127	20	58.5	1.81	1.04	8.2	1.74			124			37			31	55	

and $C(a - \bar{v})O_2$ difference had reached their maximal values, or that stroke volume was decreasing as $C(a - \bar{v})O_2$ difference was increasing. This occurred coincident with the onset of the ECG abnormalities. The steepening heart rate as $\dot{V}O_2$ increased (panel 3) is consistent with the diagnosis of myocardial ischemia. In spite of radiographic finding of interstitial lung disease and pulmonary function showing airflow obstruction, he was not limited by ventilatory factors and the noninvasive indices of pulmonary gas exchange (Table 10.69.3) were normal.

Conclusion

This patient was evaluated because of findings of chronic lung disease but was found to be limited by previously undiagnosed exercise-induced myocardial ischemia, most likely due to coronary artery disease. ECG findings of myocardial ischemia were associated with concurrent gas exchange evidence of myocardial dysfunction. The normal ventilatory equivalents indicate essentially normal ventilation–perfusion matching despite the mild obstructive and interstitial lung disease.

Case 70 Mild Interstitial Lung Disease, Silent Myocardial Ischemia, and Uncontrolled Systemic Hypertension

CLINICAL FINDINGS

This 65-year-old man had retired from work in the shipyard 5 years prior to referral for exercise testing. He had noted slight dyspnea on exertion beginning 6 years earlier but could still climb two flights of stairs without shortness of breath. He had smoked half a pack of cigarettes a day between the ages of 24 and 40. He denied cough, sputum production, or wheezing. He had recently become short of breath on a fishing trip at high altitude. At age 25, he was discharged from the Army because of a "cardiac murmur," but this was not noted on later examinations. There was no history of rheumatic fever or congestive heart failure. He took no medications. Physical examination was normal except for bilateral arcus senilis. Chest radiographs revealed bilateral pleural plaques and possible bibasilar interstitial disease.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 3 minutes. The work rate was then increased 20 W per minute. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. A resting ECG showed deep Q waves in leads II, III, and aVF compatible with an old inferior myocardial infarct. During exercise, occasional premature ventricular contractions were noted. ST-segment depression developed in leads V_4 through V_6, which reached 2 mm at a work rate of 120 W and a maximum of 4 mm at the time exercise was stopped at 160 W. The ST segments became isoelectric within 5 minutes of recovery. The patient experienced leg fatigue but denied any chest pain or discomfort.

INTERPRETATION

Comments

Results of the resting respiratory function studies were within normal limits (Table 10.70.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ was reduced, but the anaerobic threshold was within normal limits (Table 10.70.2). Proceeding to Flowchart 3 (Fig. 8.3), the breathing reserve was high (branch point 3.1). The ECG became abnormal as the maximum work rate was approached (branch point 3.3). Although the patient did not experience chest pain, the diagnosis of myocardial ischemia is supported by the marked change in slope in $\dot{V}O_2$ in response to increasing work rate (Fig. 10.70.1, panel 1) and a reduced $\Delta\dot{V}O_2/\Delta WR$. The very marked increase in R starting at 80 W (Table 10.70.3 and see Fig. 10.70.1, panel 8) reflects the development of a significant metabolic acidosis as the anaerobic threshold is exceeded. The steepening heart rate response with increasing $\dot{V}O_2$ (see Fig. 10.70.1, panel 3) and the failure of O_2 pulse to increase beyond a low work rate (see Fig. 10.70.1, panel 2) reflect a low stroke volume and a maximal $C(a - \bar{v})O_2$ being reached relatively early in the test.

Table 10.70.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		65
Sex		Male
Height (cm)		174
Weight (kg)	77	65
Hematocrit (%)		45
VC (L)	3.97	3.58
IC (L)	2.64	2.24
TLC (L)	6.21	6.68
FEV_1 (L)	3.09	2.60
FEV_1/VC (%)	78	73
MVV (L/min)	128	117
DLCO (mL/mm Hg/min)	25.6	21.7

Table 10.70.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.88	1.41
Maximum heart rate (beats/min)	155	176
Maximum O_2 pulse (mL/beat)	12.1	8.0
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.3	7.3
AT (L/min)	>0.84	1.05
Blood pressure (mm Hg [rest, max])		189/108, 234/126
Maximum $\dot{V}E$ (L/min)		74
Exercise breathing reserve (L/min)	>15	43
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.8	32.6
PaO_2 (mm Hg [rest, max ex])		93, 89
$P(A-a)O_2$ (mm Hg [rest, max ex])		15, 35
$PaCO_2$ (mm Hg [rest, max ex])		39, 40
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		3, 1
VD/VT (rest, heavy ex)		0.32, 0.37

This patient had significant untreated systemic hypertension with a rate-pressure product of over 39,000 at the time the ST-segment changes became evident. It is likely that the onset of myocardial ischemia and impaired cardiac function would have been delayed with control of blood pressure and reduction in myocardial $\dot{V}O_2$.

Ventilatory equivalents and VD/VT failed to decrease during exercise as much as expected, and the $P(A-a)O_2$, though normal at rest, increased slightly more than predicted at peak exercise. These findings suggest mild ventilation–perfusion mismatching. Although pulmonary function tests were within normal limits, there were radiographic changes suggestive of early interstitial lung disease. These mild abnormalities do not appear to contribute to exercise limitation. Elevated VD/VT and $\dot{V}E/\dot{V}CO_2$ are also characteristic of chronic heart failure, as described in Chapter 5. Thus, the differential diagnosis for the gas exchange abnormalities includes subclinical heart failure as well as interstitial lung disease.

Conclusion

This test demonstrated exercise-induced myocardial ischemia with reduced exercise performance secondary to coronary artery disease and systemic hypertension. Subtle abnormalities in pulmonary gas exchange supporting the suspicion of coexisting occupational lung disease were also evident but were not the cause of exercise limitation.

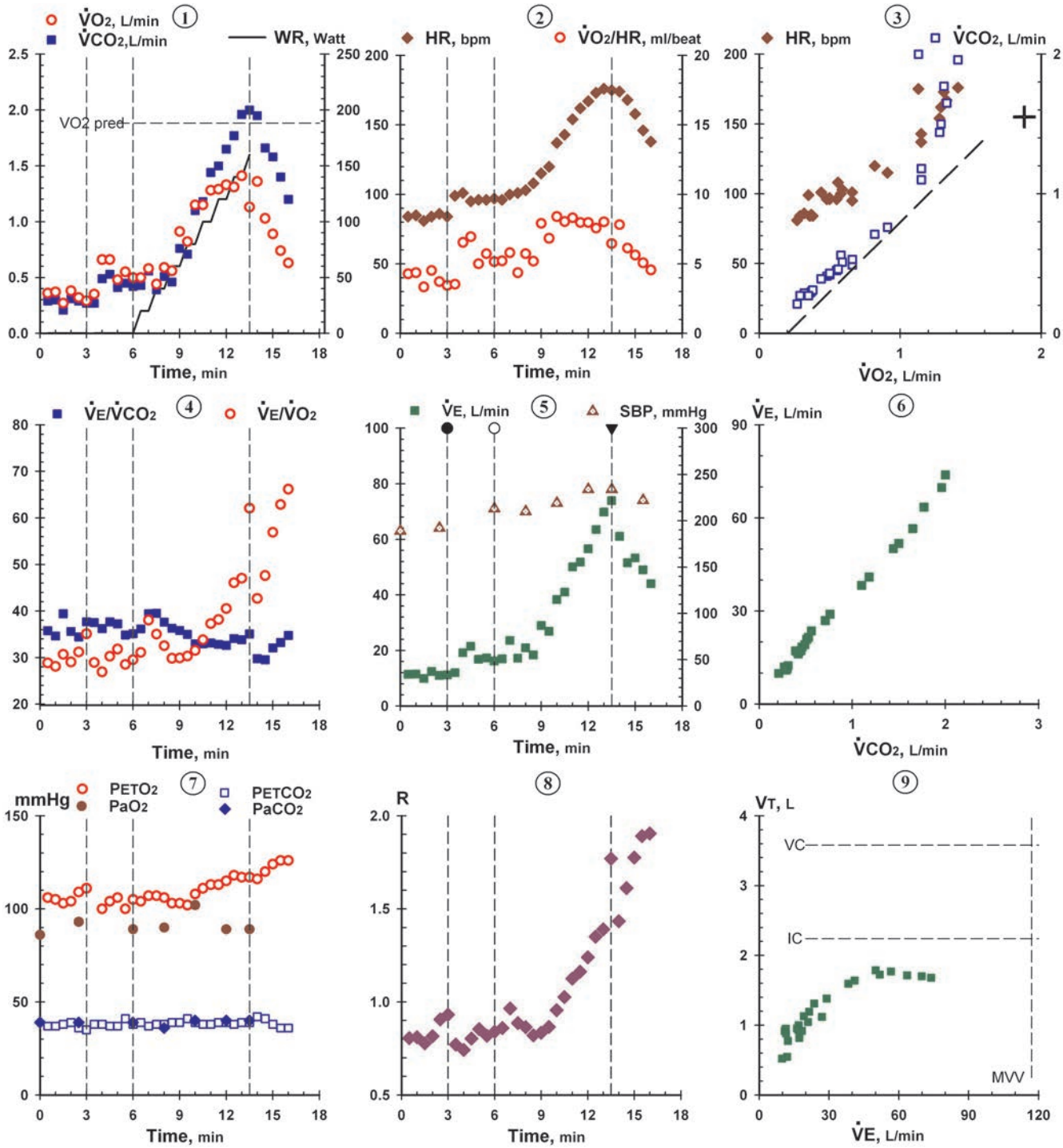

FIGURE 10.70.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.70.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	189/108								7.44	26		86			39				
0.5	Rest		84	12	11.4	0.29	0.36	4.3	0.81			106			37			36	29	
1.0	Rest		85	13	11.5	0.30	0.37	4.4	0.81			105			37			35	28	
1.5	Rest		81	19	9.9	0.21	0.27	3.3	0.78			103			38			39	31	
2.0	Rest		84	16	12.4	0.31	0.38	4.5	0.82			104			39			36	29	
2.5	Rest	192/114	86	12	11.0	0.29	0.32	3.7	0.91	7.44	26	109	93	15	36	39	3	34	31	0.32
3.0	Rest		84	12	11.2	0.27	0.29	3.5	0.93			111			35			38	35	
3.5	Unloaded		99	22	12.0	0.27	0.35	3.5	0.77			193			38			38	29	
4.0	Unloaded		101	17	19.2	0.49	0.66	6.5	0.74			100			38			36	27	
4.5	Unloaded		95	18	21.5	0.53	0.66	6.9	0.80			104			37			38	30	
5.0	Unloaded		96	18	16.8	0.41	0.48	5.0	0.85			106			37			37	32	
5.5	Unloaded		96	19	17.3	0.45	0.55	5.7	0.82			100			41			35	29	
6.0	Unloaded	213/120	97	17	16.2	0.42	0.50	5.2	0.84	7.43	25	105	89	16	38	39	1	35	30	0.34
6.5	20		96	17	17.0	0.43	0.50	5.2	0.86			104			39			36	31	
7.0	20		100	18	23.6	0.56	0.58	5.8	0.97			107			37			39	38	
7.5	30		101	21	17.2	0.39	0.44	4.4	0.89			107			38			40	35	
8.0	30	210/114	103	20	20.9	0.51	0.59	5.7	0.86	7.50	28	106	90	20	38	36	–2	38	33	0.33
8.5	60		108	20	18.4	0.46	0.56	5.2	0.82			103			39			36	30	
9.0	60		115	21	29.0	0.76	0.91	7.9	0.84			103			39			36	30	
9.5	80		120	24	26.9	0.71	0.82	6.8	0.87			102			41			35	30	
10.0	80	219/117	137	24	38.3	1.10	1.15	8.4	0.96	7.36	22	108	102	7	39	40	1	33	32	0.33
10.5	100		143	25	41.0	1.18	1.15	8.0	1.03			111			38			33	34	
11.0	100		154	28	50.1	1.44	1.28	8.3	1.13			113			38			33	37	
11.5	120		162	30	51.8	1.50	1.29	8.0	1.16			113			39			33	38	
12.0	120	234/126	167	32	56.6	1.65	1.33	8.0	1.24	7.35	22	115	89	27	39	40	1	33	41	0.32
12.5	140		173	37	63.5	1.77	1.31	7.6	1.35			118			38			34	46	
13.0	140		176	41	69.8	1.96	1.41	8.0	1.39			117			39			34	47	
13.5	160	234/126	175	44	73.9	2.00	1.13	6.5	1.77	7.35	22	117	89	35	39	40	1	35	62	0.37
14.0	Recovery		174	36	61.1	1.95	1.36	7.8	1.43			116			42			30	43	
14.5	Recovery		168	30	51.6	1.66	1.03	6.1	1.61			120			41			30	48	
15.0	Recovery		158	31	53.3	1.58	0.89	5.6	1.78			124			38			32	57	
15.5	Recovery	220/120	146	29	49.0	1.40	0.74	5.1	1.89			126			36			33	63	
16.0	Recovery		138	27	44.0	1.20	0.63	4.6	1.90			126			36			35	66	

Case 71 Mixed Disease: Aortic Stenosis, Mitral Stenosis, and Obstructive Airway Disease

CLINICAL FINDINGS

This 43-year-old welder had recent symptoms of dyspnea and chest pain at rest and on exertion and also had experienced syncope with or without preceding lightheadedness. He had cough and sputum production worsened by exertion. In addition to being exposed to welding fumes, he was an extremely heavy smoker and was diagnosed with chronic obstructive pulmonary disease. Cardiac catheterization had revealed severe aortic stenosis (1.4 cm^2 valve area), a milder degree of mitral stenosis, normal coronary arteries, and an elevated pulmonary artery pressure of 50/25 mm Hg with a pulmonary capillary wedge pressure of 16 mm Hg. Medications included an oral β-adrenergic blocker, theophylline, and an inhaled bronchodilator. Physical examination revealed murmurs consistent with his aortic and mitral valve disease but no rales or wheezes. He was referred for exercise testing to assess the relative contributions of his cardiac and pulmonary diseases to his functional impairment.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 15 W per minute to tolerance. Blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. The resting ECG was normal except for an intraventricular conduction defect. The patient had neither chest pain nor ectopy during exercise, but expiratory wheezes and frequent premature atrial and ventricular contractions were noted early in recovery. The brachial artery pressure tracing showed a delayed upstroke (200 ms to peak pressure).

INTERPRETATION

Comments

Resting respiratory function tests revealed moderately severe obstructive lung disease partially responsive to inhaled bronchodilator, and a decreased DLCO (Table 10.71.1). The carboxyhemoglobin level was elevated at 4.3%. The systemic blood pressure tracing showed a delayed upstroke and pulse pressure was low at rest. There was only a modest increase in systolic pressure with exercise.

Analysis

Using Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ and the anaerobic threshold were decreased (Table 10.71.2). Proceeding to

Table 10.71.1

Selected Respiratory Function Data

Measurement	Predicted	Before bronchodilator	After bronchodilator
Age (years)		43	
Sex		Male	
Height (cm)		171	
Weight (kg)	74	89	
Hemoglobin (g/100 mL)		15.4	
VC (L)	4.47	3.03	3.14
IC (L)	2.98	2.03	2.23
TLC (L)	6.32	6.54	
FEV_1 (L)	3.58	1.65	1.84
FEV_1/VC (%)	80	54	
MVV (L/min)	154	62	73
DLCO (mL/mm Hg/min)	27.2	19.8	

Table 10.71.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$(L/min)	2.70	1.48
Maximum heart rate (beats/min)	177	140
Maximum O_2 pulse (mL/beat)	15.3	10.6
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.3	8.5
AT (L/min)	>1.13	1.0
Blood pressure (mm Hg [rest, max ex])		96/69, 132/69
Maximum $\dot{V}E$ (L/min)		59
Exercise breathing reserve (L/min)[a]	>15	3, 14
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.4	34.4
PaO_2 (mm Hg [rest, mod ex])		84, 95
$P(A-a)O_2$ (mm Hg [rest, mod ex])		16, 14
$PaCO_2$ (mm Hg [rest, mod ex])		40, 40
$P(a-ET)CO_2$ (mm Hg [rest, mod ex])		3, 3
VD/VT (rest, max ex)		0.33, 0.32
HCO_3^- (mEq/L [rest, 2-min recov])		25, 24
Carboxyhemoglobin (%)		4.3

[a]Using prebronchodilator and postbronchodilator MVV measures, respectively.

Flowchart 4 (Fig. 8.4), the breathing reserve (branch point 4.1) was either very low or marginally low, depending on whether the prebronchodilator or postbronchodilator MVV is used in the calculation (see Table 10.71.2). The low breathing reserve and elevated exercise VD/VT (branch point 4.2) along with abnormal $P(a-ET)CO_2$ (Table 10.71.3) point to lung disease, with normal PaO_2 and $P(A-a)O_2$, as the basis of exercise limitation. However, the low anaerobic threshold and $\Delta\dot{V}O_2/\Delta$WR and low flat O_2 pulse near-end exercise (Fig. 10.71.1, panel 2) despite a β-adrenergic blockade indicate an associated impairment of the cardiac output. The patient could have pulmonary vascular disease associated with emphysema. However, the striking abnormalities in cardiovascular response, as reflected in the low flat O_2 pulse, support impairment of left ventricular function due to valve disease as the primary abnormality. The limited increase in blood pressure and the delayed arterial upslope reflect the hemodynamic effects of valvular stenosis.

Whereas the most immediate cause of this patient's limitation appears to be cardiovascular, his coexisting cardiac and pulmonary diseases likely interact to impair exercise tolerance. Left-sided heart disease resulted in a low anaerobic threshold, which, together with high VD/VT, increased the ventilatory cost of exercise and resulted in his approaching ventilatory limitation at a low level of work. Valve replacement might improve cardiac output but would not be expected to improve his obstructive lung mechanics. It might, however, improve pulmonary ventilation–perfusion matching and delay the onset of lactic acidosis, enabling a higher level of work within the persistent constraints of his breathing capacity.

Conclusion

This case demonstrates exercise intolerance due to simultaneous cardiac and lung disease. Exercise testing is helpful in understanding the separate and interactive effects of comorbid diseases in discussions regarding the indications and expectations for major therapeutic interventions.

Table 10.71.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	93/63								7.42	25		80		39					
0.5	Rest		88	13	11.9	0.30	0.37	4.2	0.81			106			36			36	29	
1.0	Rest		79	18	15.2	0.40	0.50	6.3	0.80			102			37			34	27	
1.5	Rest		91	15	9.7	0.23	0.30	3.3	0.77			105			37			37	28	
2.0	Rest		92	17	13.0	0.33	0.43	4.7	0.77			103			37			35	27	
2.5	Rest		93	16	11.1	0.27	0.34	3.7	0.79			105			37			36	29	
3.0	Rest	96/69	93	17	12.4	0.32	0.42	4.5	0.76	7.41	25	102	84	16	37	40	3	34	26	0.33
3.5	Unloaded		98	18	23.5	0.61	0.64	6.5	0.95			114			33			36	34	
4.0	Unloaded		97	15	19.6	0.54	0.61	6.3	0.89			111			34			34	30	
4.5	Unloaded		101	26	30.2	0.71	0.76	7.5	0.93			111			33			39	37	
5.0	Unloaded		102	23	29.8	0.66	0.76	7.5	0.87			112			33			42	37	
5.5	Unloaded		102	36	32.0	0.72	0.75	7.4	0.96			116			31			40	39	
6.0	Unloaded	114/75	103	28	26.4	0.63	0.70	6.8	0.90	7.46	25	112	92	19	33	36	3	38	34	0.34
6.5	15		100	25	29.1	0.71	0.78	7.8	0.91			114			32			38	35	
7.0	15		104	31	23.8	0.60	0.75	7.2	0.80			106			36			35	28	
7.5	30		105	22	29.2	0.78	0.90	8.6	0.87			106			34			35	30	
8.0	30		106	28	27.2	0.71	0.86	8.1	0.83			106			36			35	29	
8.5	45	117/78	108	26	30.1	0.82	0.94	8.7	0.87	7.43	25	111	90	18	34	38	4	34	30	0.31
9.0	45		110	31	34.0	0.90	0.99	9.0	0.91			107			37			35	32	
9.5	60		114	29	35.0	0.98	1.06	9.3	0.92			110			35			33	31	
10.0	60	114/69	117	27	38.7	1.12	1.17	10.0	0.96	7.35	22	110	95	14	37	40	3	33	31	0.32
10.5	75		121	33	45.6	1.27	1.25	10.3	1.02			115			34			34	34	
11.0	75		125	35	49.6	1.35	1.28	10.2	1.05			116			34			35	36	
11.5	90		130	32	48.0	1.37	1.30	10.0	1.05			112			37			33	35	
12.0	90	132/69	135	35	54.9	1.53	1.42	10.5	1.08			116			34			34	37	
12.5	105		140	35	59.2	1.65	1.48	10.6	1.11			118			33			34	38	
13.0	105		141	34	57.6	1.63	1.48	10.5	1.10			117			34			34	37	
13.5	Recovery		137	30	50.0	1.47	1.27	9.3	1.16			117			36			32	37	
14.0	Recovery		131	27	39.5	1.16	0.96	7.3	1.21			117			36			32	39	
14.5	Recovery	114/72	121	29	34.3	1.04	0.85	7.0	1.22	7.42	24	110	87	30	43	38	–5	31	37	0.24

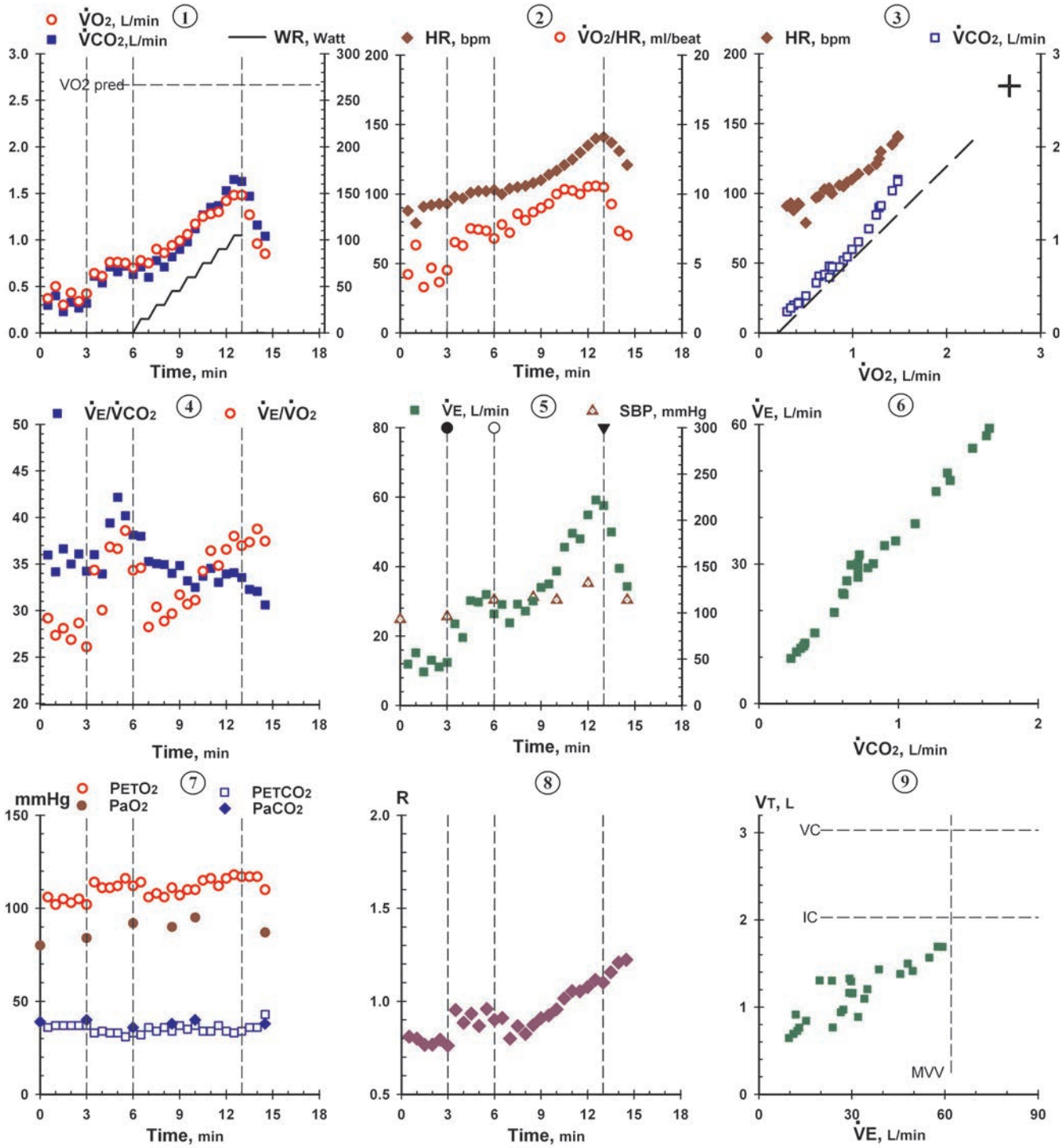

FIGURE 10.71.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 72 Mixed Disorder: Obstructive Airway Disease, Talc Pneumoconiosis, and Pulmonary Vascular Disease

CLINICAL FINDINGS

This 63-year-old man had complained of progressive dyspnea for 10 years but denied cough, sputum, wheezing, chest pain, or ankle edema. He has had hypertension for 5 years and was being treated with clonidine, triamterene, and a diuretic. For several months, he had noted epigastric burning pain, occasionally relieved by meals. He had occupational exposure to talc for over 40 years and was an ex-smoker with a 40 pack-year history of cigarette use. He had no heart murmurs. The chest radiograph showed pulmonary fibrosis. A resting ECG showed left anterior hemiblock and T-wave abnormalities in the anteroseptal region, suggestive of ischemia. The patient was referred for testing to evaluate the cause of his exertional dyspnea.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 20 W per minute to tolerance. Arterial blood was sampled every second minute, and intra-arterial pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of shortness of breath. He had no chest pain and no further ECG abnormalities.

Table 10.72.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		63
Sex		Male
Height (cm)		163
Weight (kg)	68	67
Hematocrit (%)		53
VC (L)	3.28	3.56
IC (L)	2.19	2.28
TLC (L)	5.17	6.00
FEV_1 (L)	2.55	2.20
FEV_1/VC (%)	78	62
MVV (L/min)	115	96
DLCO (mL/mm Hg/min)	23.9	10.7

INTERPRETATIONS

Comments

Resting studies showed a mild obstructive ventilatory defect with above-average lung volumes despite the fibrotic changes on chest imaging. The DLCO was severely reduced (Table 10.72.1). Blood pressure was elevated and the ECG was abnormal at rest.

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ was decreased and the anaerobic threshold was borderline abnormal (Table 10.72.2). If it is interpreted as normal, this leads to Flowchart 3 (Fig. 8.3), where the adequate breathing reserve and mildly abnormal ECG suggest the

Table 10.72.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$(L/min)	1.84	1.02
Maximum heart rate (beats/min)	157	161
Maximum O_2 pulse (mL/beat)	11.7	6.7
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.3	5.2
AT (L/min)	>0.81	0.8
Blood pressure (mm Hg [rest, max])		162/84, 249/145
Maximum $\dot{V}E$ (L/min)		66
Exercise breathing reserve (L/min)	>15	30
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.8	46.2
PaO_2 (mm Hg [rest, max ex])		79, 57
$P(A-a)O_2$ (mm Hg [rest, max ex])		33, 64
$PaCO_2$ (mm Hg [rest, max ex])		32, 33
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		4, 6
VD/VT (rest, max ex)		0.42, 0.44
HCO_3^- (mEq/L [rest, 2-min recov])		22, 17

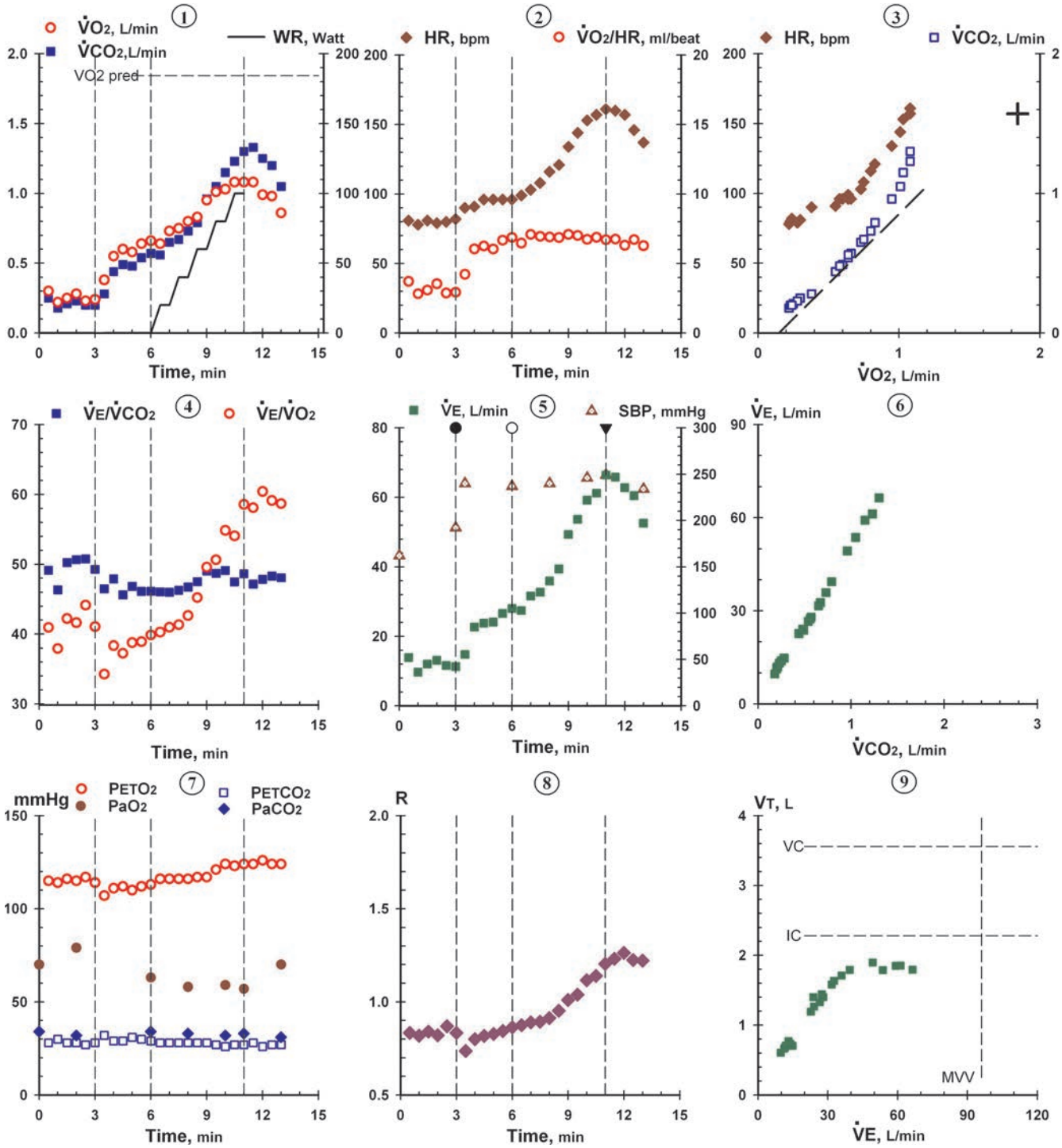

FIGURE 10.72.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

diagnosis of myocardial ischemia. This would not account for the severe gas exchange disturbances elicited, however, which include markedly abnormal V_D/V_T with high ventilatory requirements for a given metabolic rate (Fig. 10.72.1, panel 4 and Table 10.72.3). These findings are addressed by either Flowchart 4 (Fig. 8.4) or Flowchart 5 (Fig. 8.5). In Flowchart 5, for example, abnormal V_D/V_T, $P(a-ET)CO_2$, and $P(A-a)O_2$ are analyzed on right side of branch point 5.1, where the breathing reserve is used to distinguish (at branch point 5.3) between limitation due to lung disease versus cardiovascular disease. The patient's normal breathing reserve points to the latter, despite the finding of obstructive lung disease on pulmonary function testing. His progressive decline in PaO_2 during exercise leads, at branch point 5.6, to the category of pulmonary vascular disease. The findings described in the diagnostic box are consistent with his test results. These include the low $\Delta\dot{V}O_2/\Delta WR$, which decreased further near the end of the test (see Fig. 10.72.1, panel 1), very steep heart rate–$\dot{V}O_2$ relationship (see Fig. 10.72.1, panel 3), and low O_2 pulse, which remained at a subnormal level while work rate was incremented. The constellation of findings could all be accounted for by the unifying diagnosis of pulmonary vascular disease. This does not exclude the possibility that the patient had more than one condition contributing to these findings. Indeed, the pulmonary vascular disease was most likely secondary to fibrotic and obstructive lung diseases. Left-sided heart disease was also suggested by the ECG abnormalities and cardiac risk factors, and systemic hypertension may have contributed to circulatory impairment by increased afterload limiting cardiac output.

Conclusion

This patient had evidence of circulatory impairment that was more severe than expected on the basis of uncomplicated obstructive airflow disease. Comorbid interstitial disease was identified by imaging and confirmed on subsequent lung biopsy, demonstrating talc pneumoconiosis. The associated pulmonary vascular disease appeared to be the major cause of exercise limitation.

Table 10.72.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	162/84								7.43	22		70			34				
0.5	Rest		81	19	13.9	0.25	0.30	3.7	0.83			115			28			49	41	
1.0	Rest		78	16	9.7	0.18	0.22	2.8	0.82			114			30			46	38	
1.5	Rest		81	17	12.0	0.21	0.25	3.1	0.84			116			28			50	42	
2.0	Rest		79	17	13.1	0.23	0.28	3.5	0.82	7.46	22	115	79	33	28	32	4	51	42	0.42
2.5	Rest		80	17	11.6	0.20	0.23	2.9	0.87			117			27			51	44	
3.0	Rest	192/96	82	17	11.3	0.20	0.24	2.9	0.83			114			28			49	41	
3.5	Unloaded	240/117	90	21	14.8	0.28	0.38	4.2	0.74			107			32			46	34	
4.0	Unloaded		91	19	22.7	0.44	0.55	6.0	0.80			111			29			48	38	
4.5	Unloaded		96	17	23.8	0.49	0.60	6.3	0.82			112			29			46	37	
5.0	Unloaded		96	19	24.1	0.48	0.58	6.0	0.83			110			31			47	39	
5.5	Unloaded		96	20	26.6	0.54	0.64	6.7	0.84			112			30			46	39	
6.0	Unloaded	237/111	96	20	28.0	0.57	0.66	6.9	0.86	7.44	23	113	63	49	29	34	5	46	40	0.42
6.5	20		99	19	27.4	0.56	0.64	6.5	0.88			116			28			46	40	
7.0	20		103	20	31.6	0.65	0.73	7.1	0.89			116			28			46	41	
7.5	40		108	20	32.7	0.67	0.75	6.9	0.89			116			28			46	41	
8.0	40	240/114	116	21	35.9	0.73	0.80	6.9	0.91	7.45	23	116	58	56	28	33	5	47	43	0.42
8.5	60		121	22	39.4	0.79	0.83	6.9	0.95			117			28			48	45	
9.0	60		134	26	49.3	0.96	0.95	7.1	1.01			117			28			49	50	
9.5	80		144	30	53.7	1.05	1.01	7.0	1.04			121			27			49	51	
10.0	80	246/123	153	32	59.2	1.15	1.03	6.7	1.12	7.44	21	124	59	62	26	32	6	49	55	0.43
10.5	100		157	33	61.2	1.23	1.08	6.9	1.14			123			27			47	54	
11.0	100	249/145	161	37	66.4	1.30	1.08	6.7	1.20	7.40	20	124	57	64	27	33	6	49	59	0.44
11.5	Recovery		160	36	65.8	1.33	1.08	6.8	1.23			124			28			47	58	
12.0	Recovery		157	35	62.8	1.25	0.99	6.3	1.26			126			26			48	60	
12.5	Recovery		146	30	60.5	1.20	0.98	6.7	1.22			124			27			48	59	
13.0	Recovery	234/108	137	25	52.6	1.05	0.86	6.3	1.22	7.35	17	124	70	53	27	31	4	48	59	0.40

Case 73 Mixed Disorder: Peripheral Arterial Disease and Obstructive Lung Disease

CLINICAL FINDINGS

This 67-year-old man volunteered as a research subject for a study of chronic obstructive lung disease but was excluded from the research protocol because he identified calf pain, rather than dyspnea, as the limiting factor in his daily activities. He had an extensive smoking history. His only medications were inhaled bronchodilators. Examination of the lungs was notable for prolonged expiratory phase and scattered wheezes. Pulses were diminished in the right ankle. An ECG was unremarkable.

EXERCISE FINDINGS

Exercise tests were conducted on both a cycle ergometer and treadmill with an intervening rest period. On the cycle, after 2 minutes of rest, the patient pedaled at 60 rpm for 3 minutes without added resistance after which the work rate was increased continuously by 20 W per minute until he stopped with primary symptoms of right calf pain and lesser symptoms of dyspnea. For the treadmill, after 2 minutes of standing rest, the patient walked on the treadmill at 2 mph and zero grade for 3 minutes, after which the grade was increased by 2% each minute. The patient discontinued the test with the same symptoms as on the cycle. Pulse oximeter readings were 89% at rest and decreased to 86% during cycling and to 84% during treadmill walking. An ECG showed no significant changes.

Comment

Spirometry demonstrated very severe expiratory airflow obstruction (Table 10.73.1). Based on measures of systolic blood pressures in upper and lower extremities, the ankle brachial index (ABI) was calculated as 0.97 on the left (near normal) but 0.54 on the right, indicative of peripheral arterial disease.

Analysis

Results of the two tests were similar with peak $\dot{V}O_2$ reduced to around 60% of the modality-specific predicted value, and the anaerobic threshold just below the lower limit of normal with either type of exercise (Table 10.73.2). The heart rate reserve was high, consistent with termination of exercise prior to reaching maximal cardiac stress. This may occur due to either ventilatory limitation or symptoms of claudication interrupting exercise. By the patient's report, he stopped due to claudication, so peripheral arterial disease was the proximal cause of limitation. Although symptoms were localized to the right calf and the ABI was near normal in the left leg, the low $\Delta\dot{V}O_2/\Delta WR$ and early *AT* indicate a more generalized impairment in O_2 delivery and utilization. This could be due to diffuse arterial disease or may reflect concomittent pulmonary vascular impairment due to his severe obstructive lung disease. Despite the findings of cardiovascular impairment and limitation, the low breathing reserve indicated that the patient was also approaching ventilatory limitation due to chronic obstructive pulmonary disease (COPD) (Flowchart 3). The gas exchange abnormalities associated with his lung disease were evident in the low pulse oximetry values (see Table 10.73.2), which compounded the impaired oxygen delivery due to vascular obstruction that caused exercise-limiting leg pain. It is likely that V_D/V_T was elevated as well, but the elevation in $\dot{V}E/\dot{V}CO_2$ that would normally accompany this appears to have been minimized by acute respiratory acidosis, as implied by the progressive rise in end-tidal P_{CO_2} (see panel 7 in Figs. 10.73.1 and 10.73.2 and Tables 10.73.3 and 10.73.4).

Table 10.73.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		67
Sex		Male
Height (cm)		180
Weight (kg)		72
VC (L)	4.70	4.68
FEV_1 (L)	3.49	1.20
FEV_1/VC (%)	74	26
MVV (L/min)	135	48

Conclusion

This case illustrates exercise impairment in a patient with comorbid peripheral arterial and obstructive lung disease. Exercise was limited by claudication. However, ventilatory limitation with increasing P_{CO_2} during exercise, along with arterial hypoxemia, probably contributed to exercise intolerance.

Table 10.73.2

Selected Exercise Data

	Cycle		Treadmill	
Measurement	**Predicted**	**Measured**	**Predicted**	**Measured**
Peak $\dot{V}O_2$ (L/min)	1.96	1.17	2.18	1.25
Maximum heart rate (beats/min)	153	106	153	116
Maximum O_2 pulse (mL/beat)	12.8	10.8	14.2	11.1
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	6.8	10.3	—
AT (L/min)	>0.92	0.86	>1.02	0.92
Blood pressure (mm Hg [rest, max ex])		135/73, 190/134		126/80, 181/119
Maximum $\dot{V}E$ (L/min)		40		40
Exercise breathing reserve (L/min)	>15	8	>15	8
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.6	32.7	28.6	33.4
SpO_2 (% [rest, max ex])		89, 86		89, 84

Table 10.73.3

Air Breathing; Cycle Ergometer Test

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{VD}{VT}$
												ET	*a*	(*A* − *a*)	*ET*	*a*	(*a* − *ET*)			
0																				
0.5	Rest	135/73	80	20	12.4	0.23	0.27	3.3	0.86			114			31			54	47	
1.0	Rest		81	20	12.3	0.22	0.26	3.3	0.85			114			30			55	47	
1.5	Rest		84	18	12.2	0.26	0.31	3.7	0.83			111			33			48	40	
2.0	Rest		84	18	11.4	0.22	0.26	3.1	0.84			113			32			52	44	
2.5	Unloaded	135/73	89	21	17.4	0.38	0.45	5.1	0.85			110			33			45	39	
3.0	Unloaded		88	20	16.4	0.36	0.44	5.0	0.83			110			34			45	38	
3.5	Unloaded		90	17	17.0	0.40	0.48	5.3	0.84			109			35			42	36	
4.0	Unloaded	144/71	86	17	17.4	0.41	0.49	5.7	0.84			108			35			42	36	
4.5	Unloaded		82	18	18.6	0.48	0.58	7.0	0.83			107			36			39	32	
5.0	Unloaded		86	17	17.7	0.43	0.50	5.8	0.85			108			35			41	35	
5.5	8	144/71	86	17	19.1	0.48	0.57	6.6	0.85			107			36			40	34	
6.0	19		88	14	16.5	0.43	0.51	5.8	0.85			105			38			38	32	
6.5	30	147/76	89	14	18.1	0.49	0.57	6.4	0.86			105			38			37	32	
7.0	38		92	17	21.2	0.55	0.63	6.9	0.87			107			37			39	34	
7.5	48		93	17	21.7	0.57	0.65	7.0	0.88			107			37			38	34	
8.0	57		94	17	24.0	0.66	0.74	7.9	0.88			106			38			36	32	
8.5	67	169/74	97	19	24.7	0.67	0.75	7.7	0.89			106			38			37	33	
9.0	75		100	18	27.0	0.77	0.86	8.6	0.90			105			40			35	32	
9.5	85		101	17	28.2	0.85	0.90	9.0	0.94			105			41			33	31	
10.0	94		102	17	31.1	0.96	1.00	9.8	0.95			105			42			33	31	
10.5	105	190/134	104	20	32.6	1.01	1.02	9.8	0.99			106			42			32	32	
11.0	114		106	23	39.1	1.23	1.17	11.0	1.05			107			43			32	33	
11.5	Recovery		101	22	37.6	1.25	1.12	11.1	1.11			107			45			30	33	
12.0	Recovery		101	22	39.9	1.35	1.15	11.4	1.17			108			45			30	35	
12.5	Recovery		101	21	36.5	1.22	0.97	9.6	1.26			111			45			30	38	
13.0	Recovery		101	21	37.4	1.20	0.91	9.0	1.32			113			43			31	41	

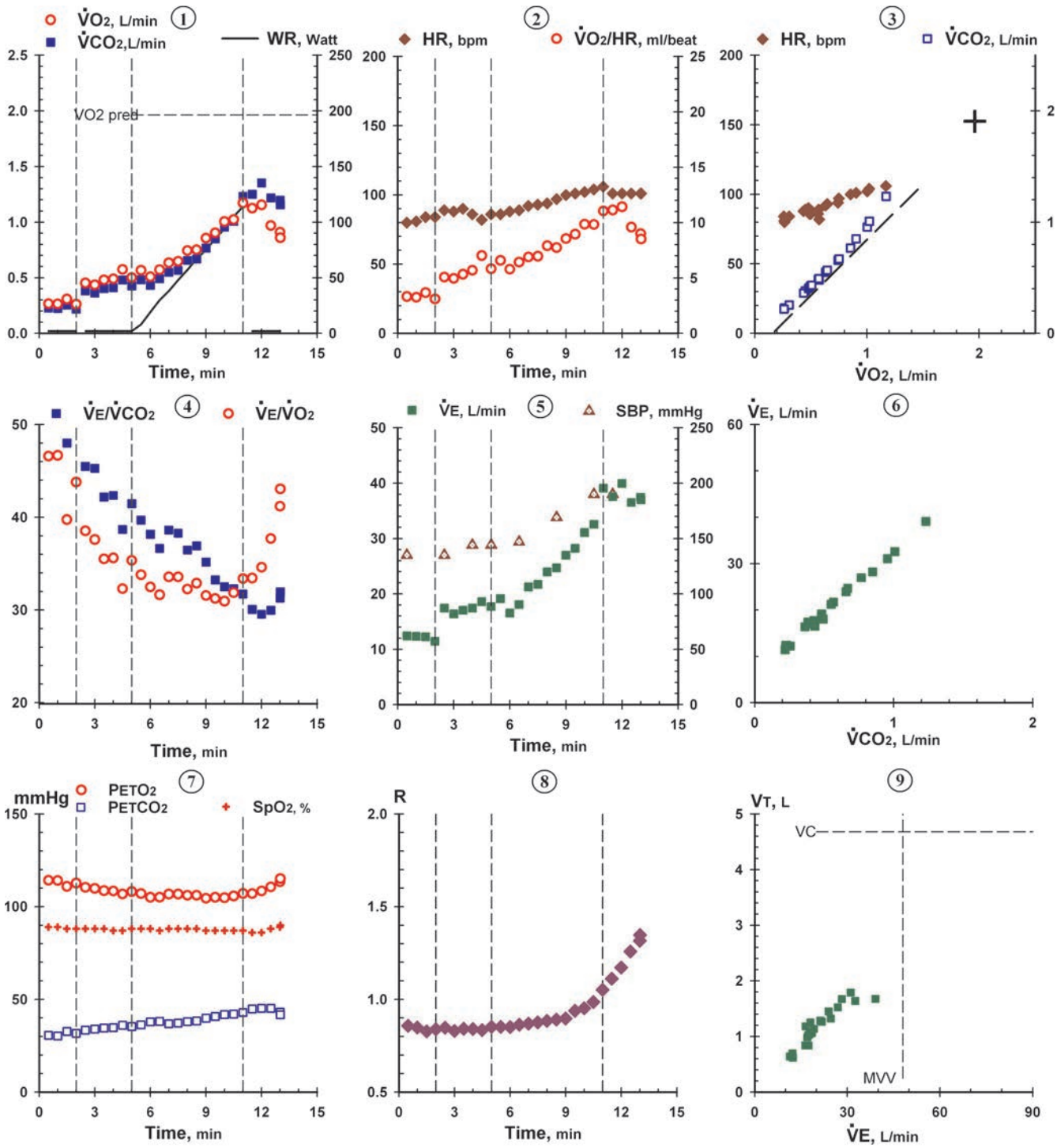

FIGURE 10.73.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

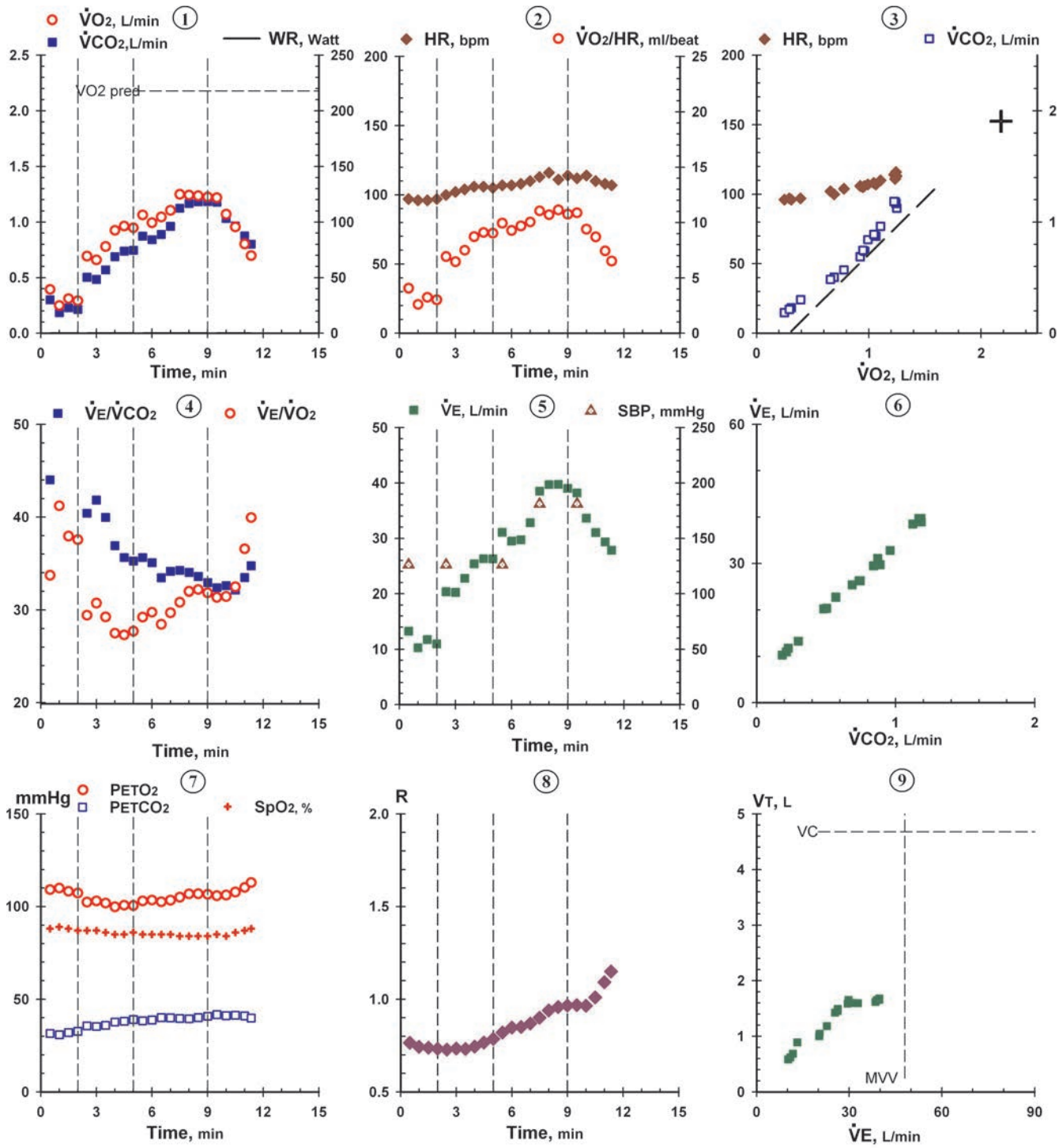

FIGURE 10.73.2. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of treadmill walking at a speed of 2 miles per hour at zero grade, the start of increasing grade by 2% per minute, and start of recovery. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.73.4

Air Breathing; Treadmill Test

Time (min)	Treadmill grade (%)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.5	Rest	126/80	97	15	13.3	0.30	0.39	4.1	0.77			109			32			44	34	
1.0	Rest		96	18	10.3	0.19	0.25	2.6	0.74			110			31			55	41	
1.5	Rest		96	17	11.8	0.23	0.31	3.2	0.74			108			32			51	38	
2.0	Rest		97	18	11.0	0.21	0.29	3.0	0.73			107			33			51	38	
2.5	0		100	19	20.4	0.50	0.69	6.9	0.73			102			36			40	29	
3.0	0		102	20	20.3	0.48	0.66	6.5	0.73			103			35			42	31	
3.5	0		104	19	22.8	0.57	0.78	7.5	0.73			102			36			40	29	
4.0	0		106	18	25.4	0.69	0.92	8.7	0.74			100			38			37	27	
4.5	0		106	18	26.3	0.74	0.96	9.1	0.77			101			38			36	27	
5.0	0		105	18	26.3	0.75	0.95	9.0	0.79			101			39			35	28	
5.5	2.0	126/78	107	19	31.1	0.87	1.06	9.9	0.82			103			38			36	29	
6.0	2.0		107	19	29.5	0.84	0.99	9.3	0.85			104			39			35	30	
6.5	4.0		108	18	29.7	0.89	1.05	9.7	0.85			103			40			33	28	
7.0	4.0		110	21	32.8	0.96	1.11	10.0	0.87			103			40			34	30	
7.5	6.0	181/119	113	24	38.5	1.12	1.25	11.1	0.90			105			40			34	31	
8.0	6.0		116	24	39.7	1.17	1.24	10.7	0.94			107			39			34	32	
8.5	8.0		111	24	39.7	1.18	1.24	11.1	0.96			107			40			34	32	
9.0	8.0		114	24	39.0	1.18	1.23	10.7	0.97			107			41			33	32	
9.5	Recovery		112	23	38.2	1.18	1.22	10.9	0.97			106			42			32	31	
10.0	Recovery		114	21	33.6	1.03	1.07	9.4	0.96			106			41			33	31	
10.5	Recovery		110	21	31.0	0.97	0.96	8.7	1.01			108			41			32	32	
11.0	Recovery		108	21	29.3	0.88	0.80	7.4	1.09			110			41			33	37	

Case 74 Exercise Testing for Staging and Prognosis in Chronic Heart Failure

CLINICAL FINDINGS

This 57-year-old woman had chronic heart failure due to left ventricular systolic dysfunction with an estimated ejection fraction of 35%. She was being treated with optimal medical therapy, including diuretics, an angiotensin converting enzyme inhibitor, a β–blocker, and statin. Exercise testing was performed to grade the severity of her impairment. On the day of testing, there were no findings of volume overload. An ECG showed a sinus rhythm with a prolonged QRS due to an intraventricular conduction delay.

EXERCISE FINDINGS

Exercise testing was conducted on a cycle ergometer. After 3 minutes of unresisted cycling at 60 rpm, the work rate was increased continuously at a rate of 10 W per minute until the patient was unable to continue. No significant ECG changes or untoward events were recorded.

Comments

Pulmonary function tests were within normal limits (Table 10.74.1). The patient was noted to have regular oscillatory changes of $\dot{V}E$, $\dot{V}O_2$, and $\dot{V}CO_2$ while seated at rest on the cycle ergometer prior to exercise. To illustrate this finding more clearly, the test data are presented as 15-second averages rather than the 30-second averages used in other cases in this chapter (Fig. 10.74.1, and Tables 10.74.2 and 10.74.3).

Table 10.74.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		57
Sex		Female
Height (cm)		168
Weight (kg)		60
VC (L)	3.27	3.01
IC (L)	2.18	2.22
FEV_1 (L)	2.64	2.55
FEV_1/VC (%)	81	85
MVV (L/min)	97	123

Analysis

The peak $\dot{V}O_2$ and anaerobic threshold are reduced relative to predicted, and the $\Delta\dot{V}O_2/\Delta WR$ slope was less than normal (Table 10.74.2). Peak heart rate was reduced, which is consistent with the use of β-blocker therapy, but the peak O_2 pulse was nevertheless lower than predicted. These findings are indicative of impairment in O_2 flow due to low stroke volume and cardiac output, as discussed in Cases 12 through 15 of this chapter, also representing patients with left ventricular systolic dysfunction. Also characteristic of chronic heart failure, the $\dot{V}E/\dot{V}CO_2$ values are high, indicating increased V_D/V_T, without evidence of arterial hypoxemia (Fig. 10.74.1, panels 4 and 7). The oscillatory pattern of VE and gas exchange variables noted at rest persisted through unloaded cycling and the early part of incremental work but became damped and inapparent above the anaerobic threshold (Fig. 10.74.1).

The peak $\dot{V}O_2$ of 14.5 mL/min/kg corresponds to Weber functional class C (>10 and <16 mL/min/kg) for grading of chronic heart failure. With medical therapies

Table 10.74.2

Selected Exercise data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.39	0.87
Peak $\dot{V}O_2$ (mL/min/kg)	23.2	14.5
Maximum heart rate (beats/min)	163	136
Maximum O_2 pulse (mL/beat)	8.5	6.7
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	7.0
AT (L/min)	>0.72	0.52
Blood pressure (mm Hg [rest, max ex])		100/60, 127/75
Maximum $\dot{V}E$ (L/min)		45
Exercise breathing reserve (L/min)	>15	78
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	29	39.4

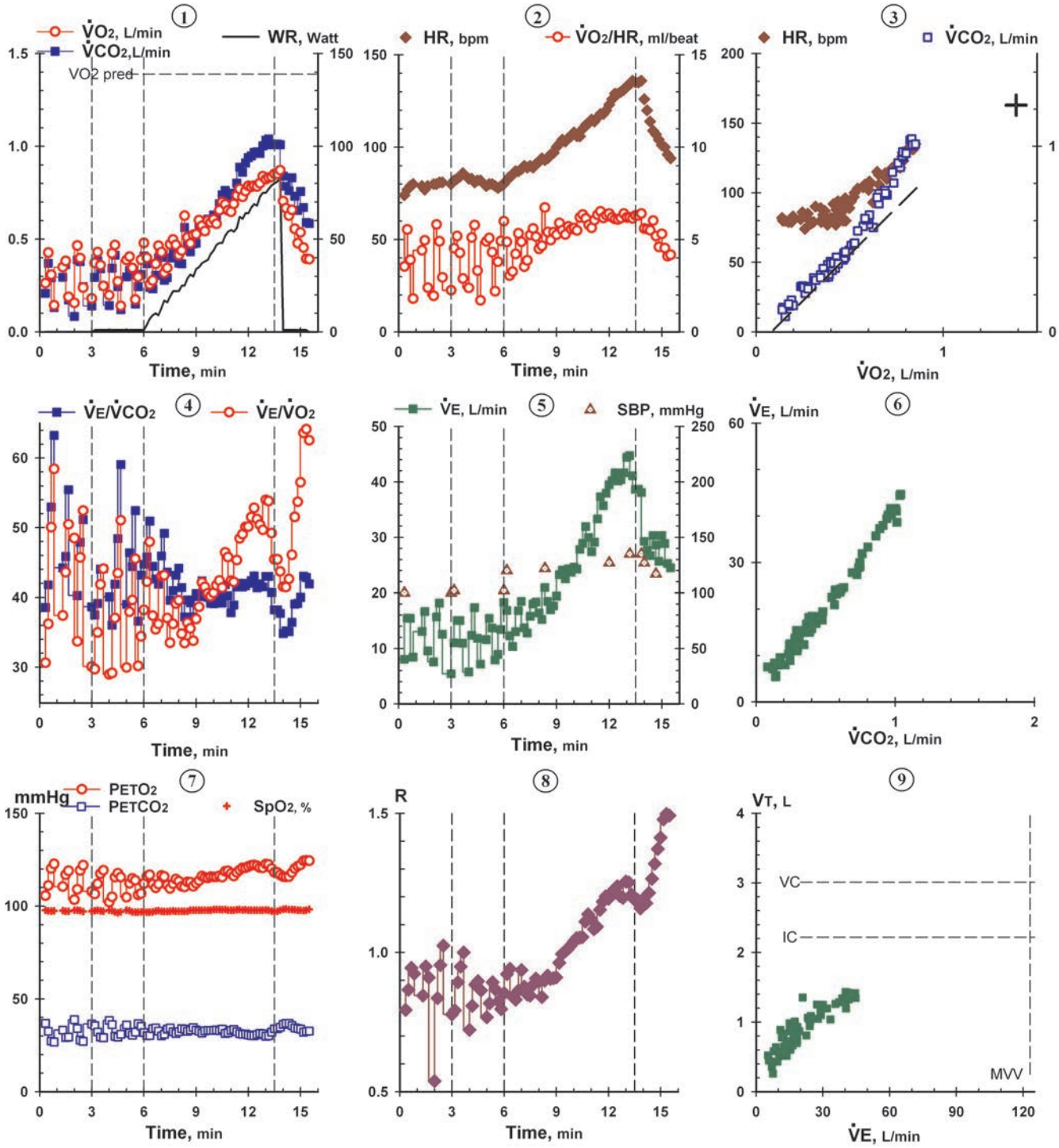

FIGURE 10.74.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject. The patient was noted to have regular oscillatory changes of V_E, $\dot{V}O_2$, and $\dot{V}CO_2$ while seated at rest on the cycle ergometer prior to exercise. To illustrate this finding more clearly, the test data are presented as 10-second averages rather than the 30-second averages used in other cases in this chapter. (Modified from Sun XG, Hansen JE, Beshai JF, et al. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. *J Am Coll Cardiol*, 2010;55:1814–1823.)

Table 10.74.3

Air Breathing (15-Second Averaging)

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0.33	Rest	100/60	74	14	8.0	0.21	0.26	3.5	0.79			106			37			39	31	
0.50	Rest		77	18	15.5	0.37	0.43	5.5	0.87			111			33			42	36	
0.67	Rest		79	25	15.4	0.29	0.31	3.9	0.94			120			27			53	50	
0.83	Rest		80	19	8.4	0.13	0.14	1.8	0.92			123			27			63	58	
1.33	Rest		79	20	13.1	0.30	0.35	4.4	0.85			111			33			44	37	
1.50	Rest		77	18	16.7	0.36	0.38	5.0	0.95			117			29			46	44	
1.67	Rest		79	22	9.5	0.17	0.19	2.4	0.91			119			30			55	50	
2.00	Rest		80	29	7.6	0.08	0.16	2.0	0.54			104			39			90	48	
2.17	Rest		80	18	15.7	0.39	0.47	5.8	0.84			109			34			40	34	
2.33	Rest		81	25	18.2	0.38	0.40	4.9	0.95			119			28			48	46	
2.50	Rest		81	19	12.5	0.25	0.24	3.0	1.03			122			27			51	52	
3.00	Rest		80	10	5.4	0.14	0.18	2.3	0.78			108			37			39	30	
3.17	Unloaded	102/66	82	20	11.0	0.29	0.37	4.5	0.79			107			36			37	30	
3.33	Unloaded		83	15	15.0	0.38	0.43	5.2	0.89			112			32			39	35	
3.50	Unloaded		84	17	15.0	0.34	0.36	4.3	0.95			117			30			44	42	
3.67	Unloaded		86	12	10.9	0.25	0.25	2.9	1.00			119			29			44	44	
4.00	Unloaded		83	13	5.7	0.14	0.20	2.4	0.72			102			38			40	29	
4.17	Unloaded		83	15	12.4	0.34	0.42	5.1	0.81			105			36			36	29	
4.33	Unloaded		81	17	17.3	0.41	0.47	5.8	0.88			116			30			42	37	
4.50	Unloaded		82	21	11.8	0.24	0.27	3.3	0.90			118			29			48	43	
4.67	Unloaded		82	20	7.1	0.12	0.14	1.7	0.86			116			31			59	51	
5.00	Unloaded		79	15	11.6	0.30	0.39	4.9	0.77			105			36			39	30	
5.17	Unloaded		80	26	15.4	0.33	0.41	5.1	0.82			112			32			46	38	
5.33	Unloaded		80	19	13.7	0.31	0.35	4.3	0.89			115			31			44	40	
5.50	Unloaded		79	18	7.9	0.15	0.17	2.2	0.87			114			32			52	46	
5.67	Unloaded		78	14	8.9	0.24	0.30	3.8	0.82			106			37			37	30	
5.83	Unloaded		79	24	13.4	0.31	0.39	4.9	0.80			107			35			43	34	
6.00	Unloaded		80	26	18.3	0.41	0.48	6.0	0.85			112			32			45	38	
6.17	4	120/80	82	21	16.9	0.37	0.40	4.9	0.92			116			30			46	42	
6.33	7		84	23	12.3	0.24	0.26	3.0	0.94			117			30			51	48	
6.50	9		85	20	10.4	0.23	0.28	3.3	0.84			112			34			44	37	
6.67	10		87	22	13.0	0.31	0.37	4.2	0.83			110			34			43	35	
6.83	9		87	22	16.8	0.40	0.46	5.3	0.86			112			33			42	36	
7.00	13		93	25	18.5	0.40	0.43	4.6	0.94			117			30			46	43	
7.17	17		90	27	13.7	0.28	0.32	3.5	0.88			116			31			49	43	
7.33	16		89	23	12.8	0.29	0.35	3.9	0.85			111			34			44	37	
7.50	19		90	22	15.8	0.40	0.47	5.2	0.85			110			34			40	33	
7.67	22		89	20	18.0	0.44	0.50	5.6	0.88			112			32			41	36	
7.83	22		91	24	18.3	0.43	0.47	5.2	0.91			115			31			43	39	
8.00	22		92	25	16.4	0.37	0.41	4.5	0.90			113			32			44	40	
8.17	25		94	21	15.2	0.37	0.44	4.7	0.84			111			34			41	35	
8.33	25	122/85	93	15	20.9	0.56	0.63	6.7	0.90			110			34			37	33	
8.50	29		94	20	18.5	0.47	0.51	5.4	0.92			113			33			40	36	
8.67	31		96	20	17.0	0.43	0.48	5.0	0.91			113			33			39	36	
8.83	30		97	20	17.7	0.48	0.52	5.4	0.91			111			35			37	34	
9.00	34		100	22	19.4	0.48	0.53	5.3	0.91			112			33			41	37	
9.17	35		102	22	23.3	0.58	0.60	5.9	0.96			114			33			40	39	
9.33	37		104	26	24.1	0.57	0.57	5.5	0.99			116			32			42	42	
9.50	38		103	28	22.5	0.55	0.54	5.3	1.00			115			33			41	41	
9.67	39		105	24	24.3	0.61	0.60	5.7	1.01			115			33			40	41	
9.83	42		106	23	23.7	0.60	0.59	5.6	1.03			116			33			39	40	
10.00	44		108	23	24.6	0.63	0.61	5.6	1.04			116			33			39	41	
10.17	47		106	24	24.3	0.61	0.58	5.5	1.05			116			33			40	42	
10.33	48		106	27	27.8	0.69	0.66	6.2	1.05			116			33			40	42	
10.50	48		110	25	28.9	0.74	0.70	6.4	1.06			116			34			39	41	
10.67	52		112	27	31.9	0.76	0.69	6.1	1.11			119			31			42	46	
10.83	54		113	24	30.0	0.75	0.66	5.8	1.14			119			32			40	46	
11.00	55		115	22	27.4	0.73	0.65	5.6	1.12			118			33			38	42	
11.17	54		114	26	29.1	0.75	0.69	6.1	1.08			116			34			39	42	
11.33	56		116	32	33.3	0.80	0.74	6.3	1.09			118			32			41	45	
11.50	62		118	29	37.3	0.89	0.77	6.5	1.15			119			31			42	48	
11.67	61		118	28	35.7	0.86	0.73	6.2	1.18			121			31			41	49	
11.83	64		120	30	38.0	0.91	0.76	6.3	1.20			121			31			42	50	

(Continued)

Table 10.74.3

Air Breathing (15-Second Averaging) *(Continued)*

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
12.00	64	127/75	123	30	39.5	0.94	0.79	6.4	1.19			121			31			42	50	
12.17	67		126	31	40.2	0.95	0.78	6.2	1.22			122			30			42	52	
12.33	69		129	31	41.6	0.97	0.79	6.1	1.23			122			30			43	53	
12.50	68		129	28	40.2	0.97	0.78	6.1	1.24			122			31			41	51	
12.67	73		130	34	40.4	0.96	0.80	6.2	1.20			121			31			42	50	
12.83	75		131	29	41.6	1.00	0.84	6.4	1.20			121			31			42	50	
13.00	75		133	31	44.4	1.03	0.82	6.2	1.26			123			30			43	54	
13.17	77	135/90	134	33	44.7	1.04	0.83	6.2	1.25			122			30			43	54	
13.33	79		136	30	41.1	1.01	0.84	6.1	1.21			120			32			41	49	
13.50	80		135	29	38.7	1.01	0.85	6.3	1.19			118			34			38	45	
13.67	81		135	29	38.7	1.01	0.85	6.3	1.19			118			34			38	45	
13.83	83		136	28	38.1	1.01	0.87	6.4	1.16			117			35			38	44	
14.00	Recovery	127/75	126	22	29.3	0.84	0.71	5.6	1.19			116			36			35	42	
14.17	Recovery		120	25	27.6	0.79	0.67	5.6	1.18			116			37			35	41	
14.33	Recovery		114	22	26.7	0.76	0.63	5.5	1.21			116			37			35	43	
14.50	Recovery		109	24	30.3	0.83	0.66	6.0	1.26			118			36			36	46	
14.67	Recovery	117/70	107	25	28.6	0.73	0.56	5.2	1.32			120			35			39	52	
14.83	Recovery		104	22	25.7	0.66	0.48	4.6	1.37			122			34			39	54	
15.00	Recovery		101	28	30.3	0.76	0.54	5.3	1.41			122			34			40	57	
15.17	Recovery		100	30	28.9	0.67	0.45	4.5	1.48			124			32			43	64	
15.33	Recovery		96	29	25.3	0.59	0.39	4.1	1.50			125			33			43	64	
15.50	Recovery		94	27	24.5	0.59	0.39	4.2	1.49			124			33			42	63	

available at the time of this patient's evaluation, this peak $\dot{V}O_2$ portended a relatively good prognosis for near-term survival and was considerably above the level of 10 to 11 mL/min/kg that would be viewed as an indication to consider heart transplantation. Other parameters from the exercise test that have prognostic value, however, are the elevated $V_E/\dot{V}CO_2$ and the presence of oscillatory breathing, both of which have been associated with increased mortality risk. The patient's severity of heart failure and ECG findings are indications for cardiac resynchronization therapy, which may improve exercise capacity in selected patients with heart failure.

Conclusion

This case is presented to illustrate the use of exercise testing for grading the severity of heart failure and identifying markers of poor prognosis.

Case 75 Exercise Testing in Preoperative Evaluation for Lung Cancer Resection

CLINICAL FINDINGS

This 62-year-old man with a long history of chronic obstructive pulmonary disease was referred for exercise testing to assess operative risk because of the finding of a malignant pulmonary nodule. The patient had quit smoking approximately 3 months earlier and was being treated aggressively with bronchodilator therapy, including oral corticosteroids. He had no known history of cardiovascular disease and stated he could walk 2 miles.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without an added load for 3 minutes. The work rate was then increased 10 W per minute to tolerance. Heart rate and rhythm were continuously monitored, and ECGs were repeatedly obtained. Blood pressure was measured with a sphygmomanometer, and arterial saturation was estimated with an ear oximeter. The patient gave an excellent effort and stopped exercise because of shortness of breath and leg fatigue. Resting and exercise ECGs and pulse oximetry (not shown) were normal.

Table 10.75.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		62
Sex		Male
Height (cm)		170
Weight (kg)	74	68
Hematocrit (%)		49
VC (L)	3.35	2.76
IC (L)	2.23	2.07
TLC (L)	5.20	5.46
FEV_1 (L)	2.62	1.28
FEV_1/VC (%)	78	46
MVV (L/min)	113	62
DLCO (mL/mm Hg/min)	22.9	20.2

INTERPRETATION

Comments

Resting studies showed a moderately severe obstructive ventilatory defect with a normal DLCO (Table 10.75.1).

Analysis

Although the patient had a low breathing reserve at the end of exercise (Table 10.75.2) and could be considered to be approaching ventilatory limitation, the dominant findings in this test were of cardiovascular impairment. Peak $\dot{V}O_2$ was reduced and the anaerobic threshold was low (Table 10.75.2). Indeed, R rose to a value over 1.0 during unloaded cycling without evidence of hyperventilation (end-tidal PCO_2 did not decrease) and remained above 1 thereafter (Fig. 10.75.1, panel 8 and Table 10.75.3), indicating excess CO_2 production because of lactic acid buffering at a low $\dot{V}O_2$. The $\Delta\dot{V}O_2/\Delta WR$ slope was also lower than normal and became progressively more abnormal at the highest work rates (Fig. 10.75.1, panel 1). During the latter part of the test, heart rate increased steeply relative to $\dot{V}O_2$ such that the O_2 pulse reached its maximal value

TABLE 10.75.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.98	1.22
Peak $\dot{V}O_2$ (mL/min/kg)	26.8	17.9
Maximum heart rate (beats/min)	158	175
Maximum O_2 pulse (mL/beat)	12.5	7.1
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	6.7
AT (L/min)	>0.87	0.6
Blood pressure (mm Hg [rest, max])		130/80, 220/110
Maximum $\dot{V}E$ (L/min)		48
Exercise breathing reserve (L/min)	>15	14
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.4	28.2
O_2 saturation, oximeter (rest, max)		96, 96

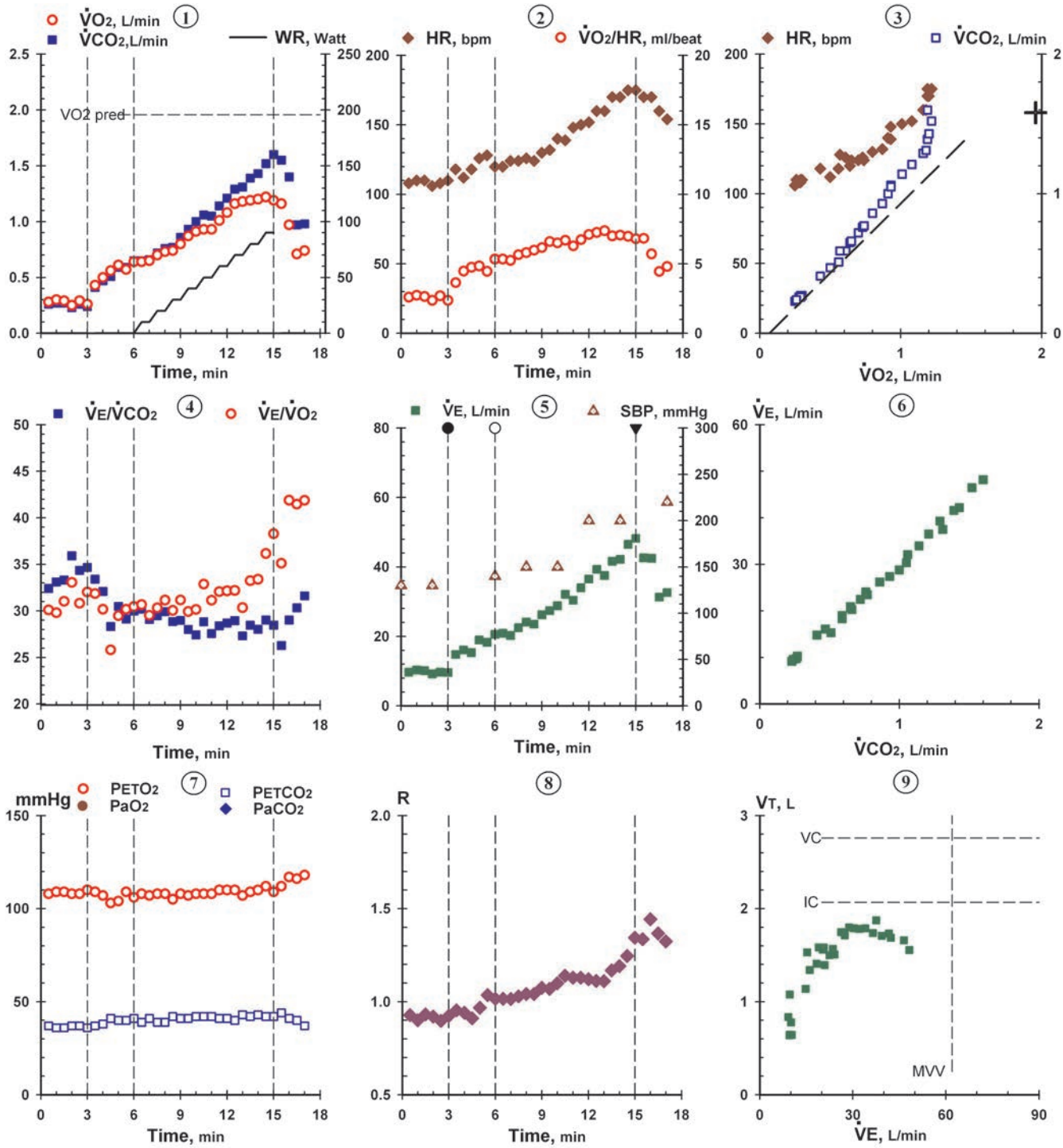

FIGURE 10.75.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 10 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.75.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
0	Rest	130/80																		
0.5	Rest		108	15	9.7	0.26	0.28	2.6	0.93			108			37			32	30	
1.0	Rest		110	16	10.3	0.27	0.30	2.7	0.90			109			36			33	30	
1.5	Rest		110	13	10.1	0.27	0.29	2.6	0.93			109			36			33	31	
2.0	Rest	130/80	106	11	9.2	0.23	0.25	2.4	0.92			108			37			36	33	
2.5	Rest		108	9	9.7	0.26	0.29	2.7	0.90			108			37			34	31	
3.0	Rest		110	15	9.6	0.24	0.26	2.4	0.92			110			36			35	32	
3.5	Unloaded		118	13	14.8	0.41	0.43	3.6	0.95			109			37			33	32	
4.0	Unloaded		112	12	16.1	0.47	0.50	4.5	0.94			107			38			32	30	
4.5	Unloaded		118	10	15.3	0.51	0.56	4.7	0.91			103			41			28	26	
5.0	Unloaded		126	12	19.0	0.59	0.61	4.8	0.97			104			40			30	29	
5.5	Unloaded		128	13	18.3	0.59	0.57	4.5	1.04			109			40			29	30	
6.0	Unloaded	140/80	120	13	20.6	0.65	0.64	5.3	1.02			106			41			30	30	
6.5	10		120	15	20.9	0.65	0.64	5.3	1.02			108			39			30	31	
7.0	10	159/90	124	13	20.3	0.66	0.65	5.2	1.02			107			41			29	30	
7.5	20		124	15	22.5	0.72	0.70	5.6	1.03			108			39			29	30	
8.0	20		126	16	24.1	0.76	0.73	5.8	1.04			108			39			30	31	
8.5	30		124	15	23.5	0.77	0.74	6.0	1.04			105			42			29	30	
9.0	30		130	15	26.2	0.86	0.80	6.2	1.08			108			41			29	31	
9.5	40		132	16	27.4	0.93	0.87	6.6	1.07			107			41			28	30	
10.0	40	150/90	140	16	28.8	1.00	0.91	6.5	1.10			108			42			27	30	
10.5	50		139	18	32.1	1.06	0.93	6.7	1.14			108			42			29	33	
11.0	50		148	17	30.4	1.05	0.93	6.3	1.13			108			42			28	31	
11.5	60		150	19	34.0	1.14	1.01	6.7	1.13			110			41			28	32	
12.0	60	200/100	152	21	36.5	1.21	1.08	7.1	1.12			110			41			29	32	
12.5	70		160	23	39.3	1.29	1.16	7.3	1.11			110			40			29	32	
13.0	70		160	20	37.5	1.31	1.18	7.4	1.11			107			43			27	30	
13.5	80		170	24	41.6	1.39	1.19	7.0	1.17			109			42			28	33	
14.0	80	200/100	170	25	42.2	1.43	1.20	7.1	1.19			110			43			28	33	
14.5	90		175	28	46.5	1.52	1.22	7.0	1.25			112			42			29	36	
15.0	90		175	31	48.2	1.60	1.19	6.8	1.34			109			42			28	38	
15.5	Recovery		170	22	42.6	1.55	1.16	6.8	1.34			112			44			26	35	
16.0	Recovery		170	22	42.5	1.40	0.97	5.7	1.44			117			41			29	42	
16.5	Recovery		160	22	31.3	0.97	0.71	4.4	1.37			116			40			30	41	
17.0	Recovery	220/110	154	19	32.6	0.98	0.74	4.8	1.32			118			37			32	42	

and remained stable over the last 2 minutes of exercise at a level well below the predicted peak value (see Fig. 10.75.1, panels 3 and 2, respectively). These abnormalities of O_2 flow were not attributable to low arterial oxygen content as evidenced by normal hematocrit and pulse oximeter values. Similarly, the $\dot{V}E/\dot{V}CO_2$ relationship was normal, implying good pulmonary V:Q matching. These findings, along with the normal DLCO, make it unlikely that the findings of cardiovascular impairment were attributable to pulmonary vascular disease complicating the patient's chronic lung disease. More likely, the patient had comorbid heart and lung diseases. There were no ECG findings to support exercise-induced ischemia, so chronic left ventricular dysfunction was suspected.

Despite the abnormal findings on this test, the peak $\dot{V}O_2$ value of 18 mL/min/kg predicted relatively little increased risk associated with resectional lung surgery. Values less than 15 mL/min/kg have been associated with increased risk of complications, and some reports suggest values of less than 10 mL/min/kg carry substantial risk of surgical morbidity and mortality.

Conclusion

This case is presented to illustrate the use of exercise testing in preoperative risk evaluations. Exercise testing is increasingly incorporated into the algorithms used for the assessment of physiologic resectability of patients with lung cancer.[1] Test results do not necessarily represent absolute indications or contraindications to potentially lifesaving procedures but do provide information for discussion of risks and benefits.

REFERENCE

1. Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemoradiotherapy). *Eur Respir J.* 2009;34(1):17–41.

Case 76 Exercise Testing for Evaluation of Work Fitness: Extreme Obesity

CLINICAL FINDINGS

This 45-year-old man was referred for an exercise study to evaluate his fitness for work as a security guard. Because of the employee's obesity, his employer was attempting to terminate him from his job on the belief that he would be unable to perform his duties, which could include running up stairs and chasing after thieves. The employee was a nonsmoker and denied any medical history, exercise limitation, or regular medications. The resting ECG was normal.

EXERCISE FINDINGS

The patient performed exercise on a treadmill because this was believed to be a better way to simulate his job functions than a cycle. He walked on the treadmill belt at 3 miles per hour (4.8 km per hour) with no grade for 3 minutes; thereafter, the grade was increased 2% per minute to tolerance. The patient appeared to give an excellent effort and stopped exercise because of fatigue; he denied chest pain or dyspnea during or after the study. No ectopy or abnormal ECG changes occurred during or after exercise.

Table 10.76.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		45
Sex		Male
Height (cm)		168
Weight (kg)	72	157
Hematocrit (%)		47
VC (L)	4.11	3.67
IC (L)	2.74	3.63
ERV (L)	1.37	0.04
FEV_1 (L)	3.31	3.19
FEV_1/VC (%)	81	87
MVV (L/min)	132	140

INTERPRETATION

Comments

Resting lung function studies are typical of extreme obesity, with reduction of the ERV but preservation of IC (Table 10.76.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1), peak $\dot{V}O_2$ and the anaerobic threshold are higher than the average predicted values when compared to reference values calculated from height and weight (Table 10.76.2). Through branch point 1.1 in this flowchart and branch points 2.1 and 2.2 in Flowchart 2 (Fig. 8.2), the findings are consistent with obesity. The breathing reserve was low at maximal exercise because of the high metabolic rate attained, but ventilatory equivalents and pulse oximetry were normal indicating normal pulmonary gas exchange. The one abnormality in the gas exchange data is the suggestion of CO_2 retention during exercise; P_{ETCO_2} increased from 40 at rest to 50 mm Hg at the lowest grade of exercise performed (Table 10.76.3). The physiologic responses to exercise otherwise appear to have been normal.

Table 10.76.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	3.28	4.14
Peak $\dot{V}O_2$ (mL/min/kg)	45.6	26.4
Maximum heart rate (beats/min)	175	191
Maximum O_2 pulse (mL/beat)	18.7	21.8
AT (L/min)	>1.39	3.25
Blood pressure (mm Hg [rest, max])		160/90, 225/100
Maximum $\dot{V}E$ (L/min)		128
Exercise breathing reserve (L/min)	>15	12
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.7	23.2

Table 10.76.3

Air Breathing; Treadmill Test

Time (min)	Treadmill grade (%)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest	160/90																		
0.5	Rest		106	20	15.2	0.45	0.60	5.7	0.75			94			42			30	23	
1.0	Rest		108	25	19.8	0.63	0.76	7.0	0.83			93			43			28	23	
1.5	Rest		113	29	16.0	0.50	0.64	5.7	0.78			89			46			27	21	
2.0	Rest	150/100	108	17	14.8	0.45	0.55	5.1	0.82			100			42			30	24	
2.5	Rest		107	20	17.7	0.55	0.69	6.4	0.80			94			42			29	23	
3.0	Rest		115	20	17.5	0.52	0.63	5.5	0.83			100			41			30	25	
3.5	0		128	35	27.1	0.81	1.20	9.4	0.68			84			44			30	20	
4.0	0		135	31	38.1	1.40	2.11	15.6	0.66			79			47			25	17	
4.5	0		141	31	51.1	1.96	2.54	18.0	0.77			81			49			25	19	
5.0	0		142	30	52.0	2.07	2.55	18.0	0.81			77			54			24	19	
5.5	0		145	33	49.2	2.01	2.43	16.8	0.83			82			53			23	19	
6.0	0	210/100	149	32	57.0	2.34	2.77	18.6	0.84			86			52			23	20	
6.5	2		152	33	59.5	2.42	2.80	18.4	0.86			74			57			23	20	
7.0	2		153	34	60.6	2.53	2.85	18.6	0.89			84			54			23	20	
7.5	4		156	34	64.6	2.66	2.96	19.0	0.90			90			51			23	21	
8.0	4	210/90	162	36	68.6	2.83	3.08	19.0	0.92			92			51			23	21	
8.5	6		162	36	72.7	2.92	3.12	19.3	0.94			88			53			24	22	
9.0	6		165	36	72.8	2.97	3.22	19.5	0.92			87			53			23	22	
9.5	8		168	40	81.1	3.28	3.43	20.4	0.96			92			52			24	23	
10.0	8	210/90	170	38	83.4	3.34	3.41	20.1	0.98			83			57			24	24	
10.5	10		175	42	88.7	3.56	3.63	20.7	0.98			90			53			24	23	
11.0	10		175	40	86.3	3.61	3.56	20.3	1.01			93			53			23	23	
11.5	12		180	43	93.6	3.79	3.64	20.2	1.04			97			51			24	25	
12.0	12	220/90	182	45	101.8	4.07	3.78	20.8	1.08			99			50			24	26	
12.5	14		186	46	106.3	4.28	3.92	21.1	1.09			99			51			24	26	
13.0	14		186	48	111.0	4.77	3.88	20.9	1.23			91			57			22	28	
13.5	16		187	52	123.5	4.75	4.08	21.8	1.16			103			49			25	29	
14.0	16	225/100	191	53	128.4	4.96	4.14	21.7	1.20			106			48			25	30	
14.5	Recovery		179	50	120.1	4.80	4.10	22.9	1.17			103			49			24	28	
15.0	Recovery	200/80	169	39	96.4	4.13	3.53	20.9	1.17			99			54			23	26	
15.5	Recovery		161	34	83.2	3.34	2.65	16.5	1.26			101			53			24	30	
16.0	Recovery	180/80	150	33	73.6	2.85	2.21	14.7	1.29			105			49			25	32	

Looking at panel 1 of Figure 10.76.1, it is apparent that the metabolic cost ($\dot{V}O_2$) of walking at 3 miles per hour on level grade was around 2.5 L per minute, which is much higher than would be the case for an individual of normal weight, and reflects the added work the patient must do to carry his excess weight. When peak $\dot{V}O_2$ is expressed in terms of liters per minute, it is higher than the predicted value (see Table 10.76.2), reflecting above-average cardiovascular capacity for oxygen delivery. When indexed to body weight, however, as milliliter per minute per kilogram, it is lower than the predicted value, reflecting below-average capacity for ambulatory work. Exercise capacity can be expressed in a number of ways; the most meaningful depends on the question being addressed by the test. In this case, it would be important to clarify whether the job requirement was that the employee be capable of chasing after thieves or that he be capable of catching them.

Conclusion

This individual's exercise test demonstrated excellent physiologic capacity, but work capacity that was compromised by the metabolic effects of obesity. The suggestion of CO_2 retention with exercise presumably reflects the increased metabolic cost of exercise and disproportionate high work of breathing.

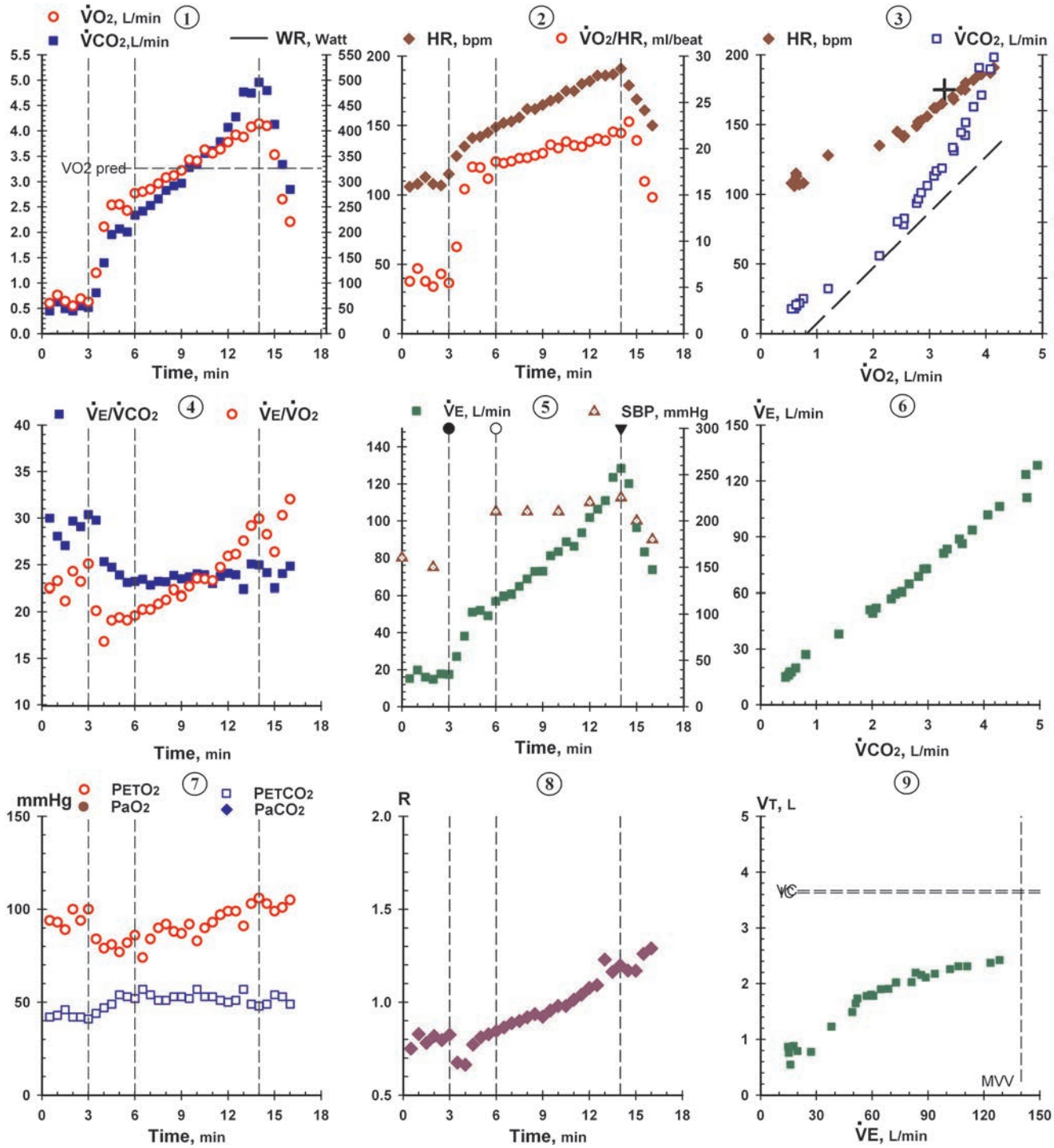

FIGURE 10.76.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of treadmill walking at a speed of 3 miles per hour at zero grade, the start of increasing grade by 2% per minute, and start of recovery. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 77 Exercise Testing for Assessment before and after Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease

CLINICAL FINDINGS

This 69-year-old man with chronic obstructive lung disease was evaluated at the time of enrollment in a pulmonary rehabilitation program to screen for contraindications to exercise training and to establish an exercise prescription. He was retested after completion of the 2-month program. The patient had recently stopped smoking after 51 years of cigarette use. His medications included theophylline and inhaled β-agonist and anticholinergic agents.

EXERCISE FINDINGS

The patient performed both incremental and constant work rate exercise tests on a cycle ergometer before and after a 2-month training period. For the incremental tests, he pedaled at 60 rpm without an added load for 3 minutes, then the work rate was increased 5 W per minute to tolerance. Heart rate and rhythm were continuously monitored; 12-lead ECGs were obtained during rest, exercise, and recovery. Samples of blood were drawn from a venous catheter placed in the back of the hand for measurement of blood lactate concentration. Constant work rate tests before and after training were performed at a work rate of 30 W. The patient was well motivated and cooperative and stopped exercise on both occasions because of dyspnea. No ECG abnormalities were noted at rest or during exercise.

INTERPRETATION

Comments

Resting pulmonary function studies showed severe obstructive lung disease, with severe loss of effective pulmonary capillary bed (Table 10.77.1).

Analysis

Referring to Flowchart 1 (Fig. 8.1) on the initial incremental study, the peak $\dot{V}O_2$ was low, and the anaerobic threshold was at the lower limits of normal (Tables 10.77.2 and 10.77.3 and Fig. 10.77.1). Regardless of which flowchart is used, the findings lead to the category of obstructive lung disease, as described in cases 45 through 52 of this chapter. Key findings include high $\dot{V}E/\dot{V}CO_2$ values, implying high VD/VT values and low breathing reserve. Typical of patients with chronic obstructive pulmonary disease (COPD), the *AT* was a relatively high proportion of the peak $\dot{V}O_2$, not because the *AT* was high but because peak $\dot{V}O_2$ was limited to a low level by the patient's low breathing capacity.

Table 10.77.1

Selected Respiratory Function Data before and after Training

Measurement	Predicted	Measured	
Age (years)		69	
Sex		Male	
Height (cm)		170	
Weight (kg)	60	74	
Hematocrit (%)		40	
		Before training	After training
VC (L)	3.60	1.99	2.19
IC (L)	2.40	1.50	1.65
FEV_1 (L)	2.78	0.99	1.11
FEV_1/VC (%)	77	50	51
MVV, indirect(L/min)	111	40	44
DLCO (mL/mm Hg/min)	22.4	10.6	12.7

Aerobic or endurance exercise training prescriptions commonly identify a training work rate that elicits a $\dot{V}O_2$ between the anaerobic threshold and peak $\dot{V}O_2$, performed for 30 to 60 minutes, 3 or more days per week. Once the targeted exercise durations are achieved and exercise tolerance begins to improve, the training stimulus can be maintained by titrating up the work rate. In this case, the rehabilitation prescription included cycle exercise at 25 W for 45 minutes per day, 3 days per week. Because his *AT* was high in proportion to peak $\dot{V}O_2$, the initial training work rate of 25 W was close to his maximum tolerance.

Following training, the incremental exercise test (Fig. 10.77.2 and Table 10.77.4) demonstrated increased peak $\dot{V}O_2$ and peak work rate and a lower end exercise

Table 10.77.2

Selected Exercise Data before and after Training

Measurement	Predicted	Before	After
Peak $\dot{V}O_2$ (L/min)	1.67	0.90	1.0
Maximum heart rate (beats/min)	151	136	140
Work rate (max W)		30	50
Maximum O_2 pulse (mL/beat)	11.1	6.6	7.6
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	11.1	8.2
AT (L/min)	>0.75	0.75	Indeterminate[a]
Maximum $\dot{V}E$ (L/min)		40	42
Exercise breathing reserve (L/min using indirect MVV)	>15	0	2
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	29.1	41.5	37.4
Peak lactate (mEq/L)		3.0	2.3

[a]Apparently, because of the small increase in lactate after training, a break point in the V-slope plot (see Fig. 10.77.1, panel 3) was not observed.

blood lactate concentration (see Table 10.77.2 and Figs. 10.77.1 and 10.77.2). The peak exercise $\dot{V}E$ was very similar between the two tests, however, as there was little change in lung mechanics. The delay of onset of lactic acidosis (compare panels 3 of Figs. 10.77.1 and 10.77.2) reduced ventilatory requirements, and so delayed the point at which exercise was terminated on the incremental test due to attainment of maximal breathing capacity. In addition, there was a decrease in $\dot{V}E/\dot{V}CO_2$ following training (compare panels 4 of Figs. 10.77.1 and 10.77.2). This is likely due to a change in the patient's breathing pattern, which was characterized by slower breathing frequency and higher tidal volume (Tables 10.77.3 and 10.77.4), or possibly improved perfusion of ventilated lung after training. Data from the constant work rate studies (Table 10.77.5) show that at the same work rate of 30 W, both $\dot{V}E$ and blood lactate concentrations were lower on the posttraining study, which is further evidence that the training had increased the patient's anaerobic threshold.

Conclusion

This case is presented as an illustration of the use of exercise testing to monitor the effects of exercise training or rehabilitation. The initial test serves to screen patients for adverse findings that should be addressed before training such as uncontrolled hypertension or exercise-induced myocardial ischemia. In addition, it provides an objective measure of baseline function for planning the exercise prescription. The case also illustrates classic training effects, which include increases in anaerobic threshold and peak $\dot{V}O_2$, and the effect that the reduced lactic acidosis has on ventilatory requirements in a patient with ventilatory limitation.

Table 10.77.3

Before Training

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest		110	13	18.0	0.39	0.43	3.9	0.91			117			28			43	39	
0.5	Rest		110	11	14.7	0.31	0.33	3.0	0.94			118			28			44	42	
1.0	Rest		111	16	15.4	0.29	0.32	2.9	0.91			118			28			48	44	
1.5	Rest		112	12	16.6	0.34	0.37	3.3	0.92			118			28			46	42	
2.0	Rest		111	14	14.8	0.27	0.29	2.6	0.93			120			26			50	47	
2.5	Rest		112	11	14.0	0.28	0.30	2.7	0.93			119			27			47	44	
3.0	Unloaded		114	25	16.6	0.28	0.33	2.9	0.85			113			31			52	44	
3.5	Unloaded		114	25	20.7	0.38	0.46	4.0	0.83			113			31			49	40	
4.0	Unloaded		115	24	23.1	0.45	0.54	4.7	0.83			112			31			47	39	
4.5	Unloaded		116	29	23.0	0.44	0.53	4.6	0.83			111			32			47	39	
5.0	Unloaded		116	25	25.2	0.52	0.61	5.3	0.85			113			31			44	38	
5.5	Unloaded		117	25	26.0	0.54	0.60	5.1	0.90			113			32			44	40	
6.0	5		118	23	25.6	0.56	0.62	5.3	0.90			113			32			42	38	
6.5	5		120	28	26.2	0.53	0.57	4.8	0.93			115			31			45	42	
7.0	10		121	27	27.0	0.56	0.60	5.0	0.93			114			32			44	41	
7.5	10		122	27	28.9	0.62	0.66	5.4	0.94			115			32			43	40	
8.0	15		124	25	29.8	0.66	0.70	5.6	0.94			113			33			42	40	
8.5	15		125	28	31.6	0.68	0.72	5.8	0.94			114			33			43	41	
9.0	20		126	29	32.8	0.72	0.74	5.9	0.97			115			32			42	41	
9.5	20		130	30	34.7	0.75	0.76	5.8	0.99			116			32			43	42	
10.0	25		131	30	33.9	0.77	0.78	6.0	0.99			115			33			41	40	
10.5	25		134	33	36.9	0.81	0.81	6.0	1.00			116			32			42	42	
11.0	30		135	31	36.9	0.84	0.84	6.2	1.00			115			34			41	41	
11.5	30		136	32	39.7	0.92	0.90	6.6	1.02			115			34			40	41	
12.0	Recovery		134	32	38.5	0.88	0.85	6.3	1.04			116			33			41	42	
12.5	Recovery		130	31	35.9	0.78	0.73	5.6	1.07			119			31			43	46	
13.0	Recovery		126	25	30.7	0.68	0.62	4.9	1.10			118			32			42	46	
13.5	Recovery		124	29	27.6	0.54	0.48	3.9	1.13			122			29			47	52	

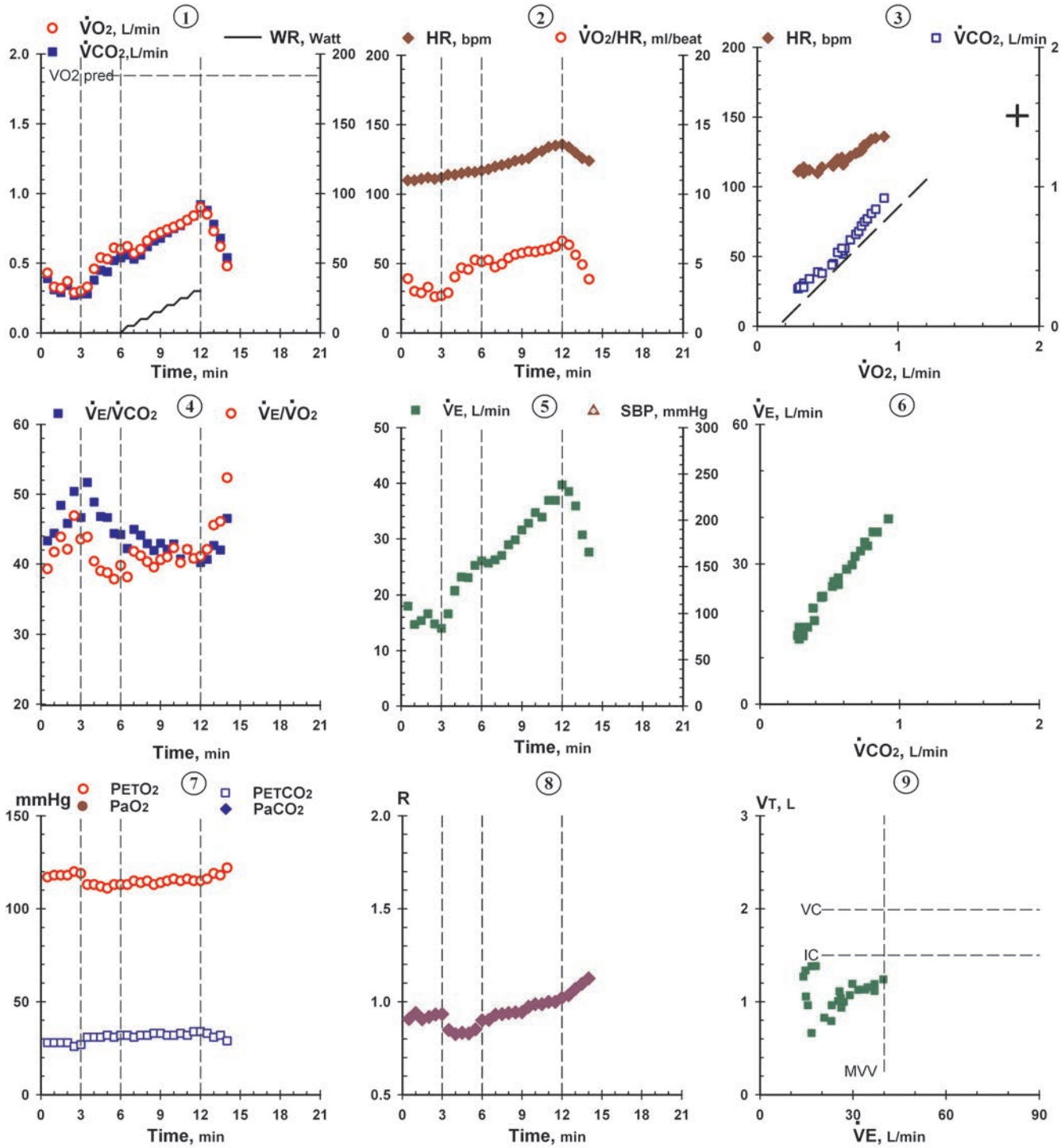

FIGURE 10.77.1. Before training test. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 5 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

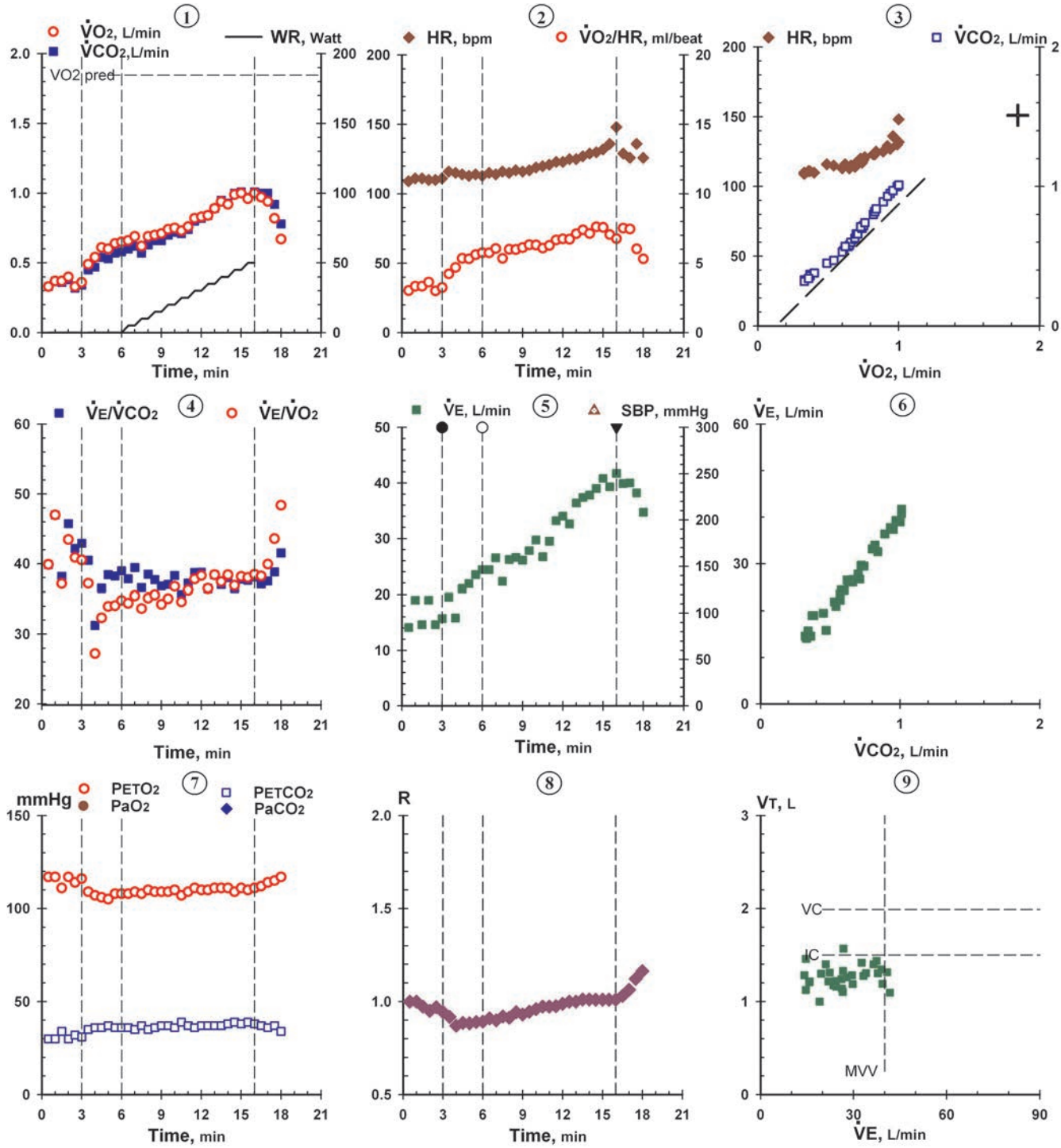

FIGURE 10.77.2. After training test. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 5 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and P_{ETCO_2} (**panel 7**) is not decreasing, simultaneously. The *black* + *symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Table 10.77.4

After Training

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}_{CO_2}$ (L/min STPD)	$\dot{V}_{O_2}$ (L/min STPD)	$\frac{\dot{V}_{O_2}}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}_E}{\dot{V}_{CO_2}}$	$\frac{\dot{V}_E}{\dot{V}_{O_2}}$	$\frac{V_D}{V_T}$
												ET	a	(A − a)	ET	a	(a − ET)			
0	Rest		109	11	14.1	0.33	0.33	3.0	1.00			117			30			40	40	
0.5	Rest		111	19	19.0	0.37	0.37	3.3	1.00			117			30			47	47	
1.0	Rest		111	10	14.6	0.36	0.37	3.3	0.97			111			34			38	37	
1.5	Rest		110	19	19.0	0.38	0.40	3.6	0.95			117			30			46	43	
2.0	Rest		110	13	14.6	0.32	0.33	3.0	0.97			114			32			42	41	
2.5	Rest		111	13	15.7	0.34	0.36	3.2	0.94			116			31			43	41	
3.0	Unloaded		116	15	19.5	0.45	0.49	4.2	0.92			109			35			41	37	
3.5	Unloaded		115	13	15.8	0.47	0.54	4.7	0.87			107			36			31	27	
4.0	Unloaded		114	15	21.0	0.54	0.61	5.4	0.89			106			36			37	32	
4.5	Unloaded		113	18	21.9	0.53	0.60	5.3	0.88			105			37			38	34	
5.0	Unloaded		114	20	23.5	0.57	0.64	5.6	0.89			108			36			38	34	
5.5	Unloaded		113	21	24.4	0.58	0.65	5.8	0.89			108			36			39	35	
6.0	5		115	20	24.4	0.60	0.66	5.7	0.91			108			36			38	34	
6.5	5		114	24	26.5	0.62	0.69	6.1	0.90			109			35			39	35	
7.0	10		116	17	22.3	0.57	0.62	5.3	0.92			108			37			37	34	
7.5	10		115	23	26.2	0.63	0.69	6.0	0.91			110			35			38	35	
8.0	15		117	20	26.6	0.66	0.70	6.0	0.94			109			36			38	36	
8.5	15		116	21	26.1	0.66	0.71	6.1	0.93			109			37			37	34	
9.0	20		117	22	27.8	0.70	0.74	6.3	0.95			109			37			37	35	
9.5	20		119	25	29.7	0.72	0.75	6.3	0.96			110			36			38	37	
10.0	25		120	17	26.7	0.71	0.73	6.1	0.97			107			39			36	35	
10.5	25		121	23	29.5	0.74	0.76	6.3	0.97			109			37			37	36	
11.0	30		123	26	33.2	0.80	0.82	6.7	0.98			111			36			39	38	
11.5	30		123	26	34.0	0.82	0.83	6.7	0.99			110			37			39	38	
12.0	35		125	23	32.6	0.84	0.84	6.7	1.00			110			37			36	36	
12.5	35		125	26	36.4	0.89	0.89	7.1	1.00			111			37			38	38	
13.0	40		127	26	37.4	0.95	0.94	7.4	1.01			111			37			37	37	
13.5	40		129	29	37.8	0.93	0.92	7.1	1.01			111			38			38	38	
14.0	45		130	29	39.0	1.00	0.99	7.6	1.01			109			39			37	37	
14.5	45		132	31	40.8	1.01	1.00	7.6	1.01			111			38			38	38	
15.0	50		136	33	39.3	0.97	0.96	7.1	1.01			110			39			38	38	
15.5	50		148	38	41.7	1.01	1.00	6.8	1.01			111			38			38	38	
16.0	Recovery		129	33	39.9	1.00	0.97	7.5	1.03			112			37			37	38	
16.5	Recovery		126	29	40.0	1.00	0.94	7.5	1.06			114			36			38	40	
17.0	Recovery		136	29	38.2	0.92	0.82	6.0	1.12			115			37			39	44	
17.5	Recovery		126	27	34.7	0.78	0.67	5.3	1.16			117			34			42	48	

Table 10.77.5

Selected Data from Constant Work Rate Tests

	Responses to 30 Watts	
	Before rehabilitation	After rehabilitation
$\dot{V}_E$ (L/min)	40	34
$\dot{V}_{O_2}$ (L/min)	0.90	0.83
$\dot{V}_{CO_2}$ (L/min)	0.92	0.82
Heart rate (bpm)	136	123
Lactate (mEq/L)	3.0	1.7

Case 78 Evaluation of Unexplained Dyspnea: A Morbidly Obese Asthmatic

CLINICAL FINDINGS

This 55-year-old man was referred for cardiopulmonary exercise testing for evaluation of unexplained dyspnea that had not improved with escalation of his asthma therapy. Although he reported symptoms for the preceding 6 to 12 months, he also indicated that his weight had increased by 80 lb several years previously, which he attributed to curtailing his activities due to exertional dyspnea. He was morbidly obese and was treated for hypertension, adult onset diabetes, and obstructive sleep apnea. He had an episode of deep vein thrombosis several years previously without known pulmonary embolism. He worked in an office and was short of breath even with sustained walking indoors; he did no recreational activities. His medications included a diuretic, an angiotensin-converting enzyme (ACE) inhibitor, oral hypoglycemic agents, inhaled corticosteroids and long-acting β-agonist, a leukotriene modifier, warfarin anticoagulation, and nocturnal continuous positive airway pressure. His examination was notable only for obesity with a body mass index (BMI) of 45. The ECG showed a sinus rhythm and was normal.

EXERCISE FINDINGS

The patient exercised on a cycle ergometer beginning with 3 minutes of pedaling without an added load, followed by an increase in work rate by 15 W per minute to tolerance. He cooperated well with the study and ended the test with symptoms of leg fatigue and dyspnea. Because of the history of airflow obstruction, spirometry was repeated serially for 20 minutes after exercise. Spontaneous flow-volume loops were monitored on a breath-by-breath basis during exercise, and inspiratory capacity was measured periodically to identify the occurrence of dynamic hyperinflation.

Comments

On the day of testing, pulmonary function tests showed a mild restrictive defect, but no evident obstruction, and a normal DLCO (Table 10.78.1). The restrictive defect was characteristic of obesity, rather than pulmonary fibrosis, in that the ERV was markedly reduced and IC was elevated.

Analysis

Peak $\dot{V}O_2$ and *AT* were mildly reduced relative to predicted (Table 10.78.2). The weight-indexed $\dot{V}O_2$ was even lower, due to the combined effects of low peak $\dot{V}O_2$ and excess weight. The ventilatory and gas exchange responses to exercise were normal, including a large breathing reserve, normal oximetry, and normal $\dot{V}E/\dot{V}CO_2$ at the *AT* (see Table 10.78.2 and Fig. 10.78.1). In addition, the inspiratory capacity remained stable during exercise, and postexercise spirometry was unchanged from rest

Table 10.78.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		55
Sex		Male
Height (cm)		185
Weight (kg)		169
VC (L)	5.44	4.26
IC (L)	3.62	3.98
FEV_1 (L)	4.16	3.01
FEV_1/VC (%)	77	71
MVV (L/min)	157	120

Table 10.78.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	3.04	2.17
Peak $\dot{V}O_2$ (mL/min/kg)	40.5	12.8
Maximum heart rate (beats/min)	165	96
Maximum O_2 pulse (mL/beat)	18.5	23.1
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	9.2
AT (L/min)	>1.39	1.28
Blood pressure (mm Hg [rest, max])		132/83, 195/84
Maximum $\dot{V}E$ (L/min)		72
Exercise breathing reserve (L/min)	>15	48
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	27.2	27.4

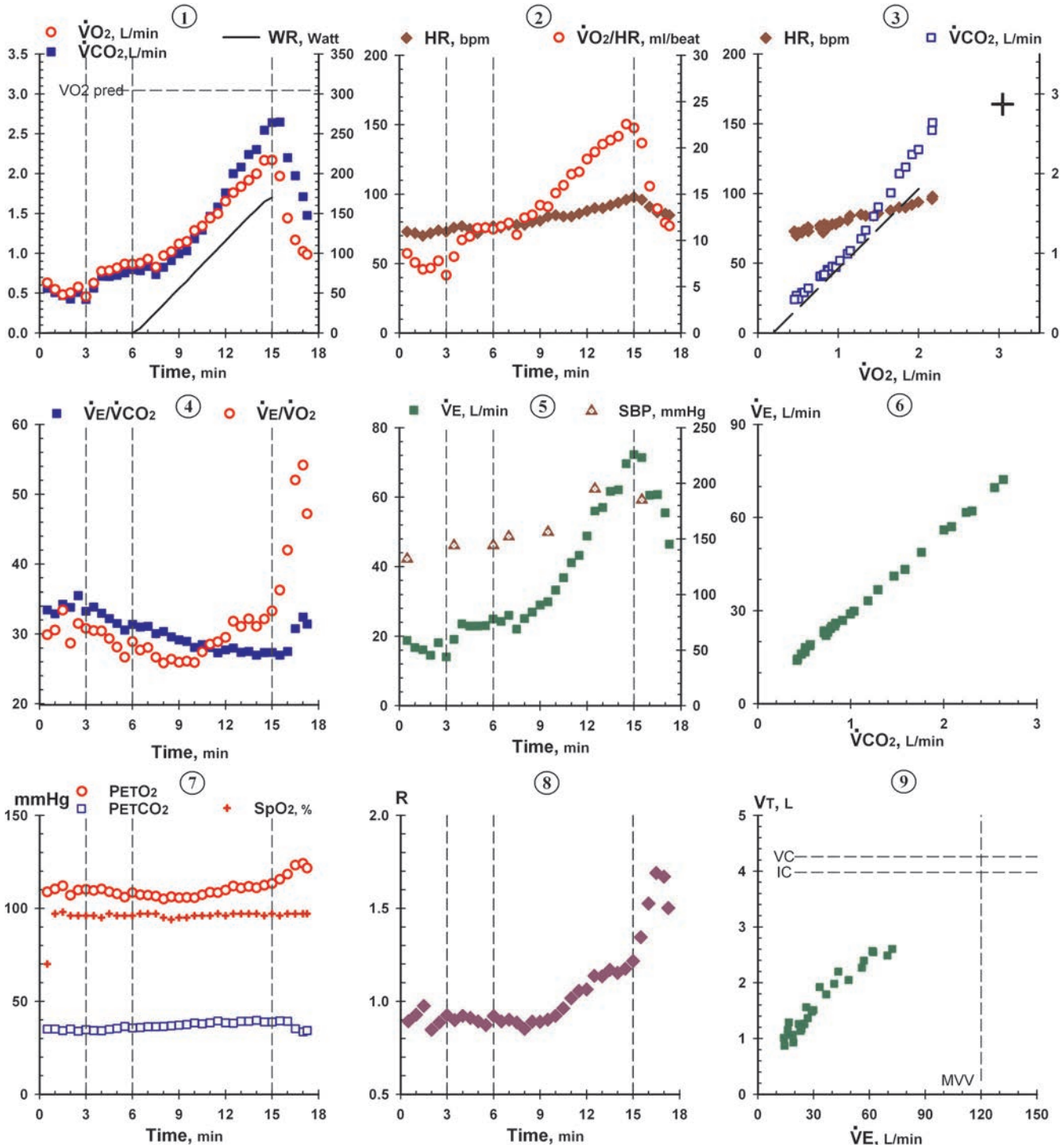

FIGURE 10.78.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

(data not shown). These findings argue against occult pulmonary vascular disease or poorly controlled asthma as the cause of his symptoms.

The one abnormal finding in this test was the patient's impaired heart rate response to exercise (see Fig. 10.78.1, panel 2). The cardiac rhythm remained sinus, and there were no ischemic changes. It is clear that the highly attenuated heart rate response was not the result of poor effort, as the patient exercised considerably past his lactate threshold as shown by the V slope (see Fig. 10.78.1, panel 3) and reflected in an end-exercise R of over 1.2 (Table 10.78.3 and Fig. 10.78.1, panel 8). Also, the heart rate response was shallow relative to $\dot{V}O_2$ across the entire range of the test (see Fig. 10.78.1, panel 3). The peak O_2 pulse was much higher than predicted, implying a compensatory increase in stroke volume, which partially offsets the effect of the low heart rate on oxygen delivery and indicates excellent systolic function. The patient's medication history was again reviewed in detail to confirm that he was not taking a β-blocker or other agent that would affect heart rate. As he was not receiving any medication that could account for these findings, it was concluded that he had intrinsic chronotropic insufficiency due to sinus node disease.

Conclusion

This test is presented as an example of a specific diagnosis being identified by exercise testing for evaluation of unexplained dyspnea. The potential causes of dyspnea in this case were diverse, including obesity, deconditioning, reactive airway disease, or unrecognized thromboembolism, as well as cardiovascular disease. If the testing had been performed without gas exchange measurements, the low peak heart rate might have been interpreted as an inadequate effort. The relationship of heart rate and $\dot{V}O_2$ allowed confident identification of chronotropic insufficiency as the cause of exercise intolerance.

Table 10.78.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}_E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg ET	P_{O_2}, mm Hg a	P_{O_2}, mm Hg (A − a)	P_{CO_2}, mm Hg ET	P_{CO_2}, mm Hg a	P_{CO_2}, mm Hg (a − ET)	$\frac{\dot{V}_E}{\dot{V}CO_2}$	$\frac{\dot{V}_E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
0																				
0.5	Rest	132/83	73	18	18.8	0.56	0.63	8.6	0.89			109			35			33	30	
1.0	Rest		72	13	16.8	0.51	0.55	7.6	0.93			110			35			33	31	
1.5	Rest		70	14	16.1	0.47	0.48	6.9	0.98			112			34			34	33	
2.0	Rest		72	17	14.5	0.43	0.51	7.0	0.85			107			35			34	29	
2.5	Rest		74	17	18.1	0.51	0.58	7.8	0.89			110			34			35	31	
3.0	Rest		73	14	14.0	0.42	0.46	6.2	0.93			110			35			33	31	
3.5	Unloaded	144/79	76	21	19.1	0.56	0.63	8.3	0.90			110			34			34	30	
4.0	Unloaded		77	20	23.6	0.71	0.77	10.1	0.92			110			34			33	30	
4.5	Unloaded		75	20	22.9	0.71	0.78	10.4	0.91			109			35			32	29	
5.0	Unloaded		72	19	22.9	0.73	0.82	11.3	0.89			108			36			32	28	
5.5	Unloaded		76	18	23.1	0.76	0.87	11.4	0.87			106			36			31	27	
6.0	Unloaded		77	20	25.0	0.80	0.86	11.2	0.92			108			36			31	29	
6.5	6	152/73	76	19	24.3	0.78	0.88	11.5	0.89			107			36			31	28	
7.0	16		78	17	26.0	0.84	0.93	11.9	0.90			107			36			31	28	
7.5	26		78	18	22.1	0.73	0.83	10.6	0.89			107			36			30	27	
8.0	36		78	20	25.1	0.83	0.97	12.4	0.85			105			37			30	26	
8.5	46		80	20	26.9	0.91	1.02	12.8	0.89			106			37			30	26	
9.0	56		81	20	29.0	1.00	1.12	13.8	0.89			106			37			29	26	
9.5	65	156/79	84	20	29.9	1.03	1.15	13.7	0.90			106			38			29	26	
10.0	76		85	17	33.3	1.18	1.28	15.1	0.92			106			38			28	26	
10.5	86		84	21	36.8	1.29	1.34	16.0	0.96			107			38			28	27	
11.0	96		84	21	41.1	1.47	1.44	17.2	1.02			109			38			28	29	
11.5	106		86	20	43.2	1.58	1.50	17.4	1.06			108			39			27	29	
12.0	116		88	24	48.8	1.76	1.65	18.8	1.06			110			39			28	30	
12.5	126	195/68	90	25	56.0	2.00	1.76	19.6	1.14			112			38			28	32	
13.0	136		90	24	57.1	2.08	1.84	20.4	1.13			111			39			27	31	
13.5	146		92	24	61.7	2.24	1.92	20.8	1.17			112			39			28	32	
14.0	155		94	24	62.1	2.30	2.00	21.2	1.15			111			40			27	31	
14.5	165		94	28	69.6	2.55	2.17	20.1	1.18			112			39			27	32	
15.0	170		94	28	72.3	2.64	2.17	23.1	1.22			113			39			27	33	
15.5	Recovery	185/84	96	27	71.4	2.65	1.97	20.5	1.34			116			40			27	36	
16.0	Recovery		91	21	60.5	2.20	1.44	15.8	1.53			118			39			27	42	
16.5	Recovery		87	23	60.8	1.97	1.17	13.4	1.69			123			35			31	52	
17.0	Recovery		86	21	55.5	1.71	1.02	11.9	1.67			124			34			32	54	

Case 79 Evaluation of Unexplained Dyspnea: Thromboembolic Pulmonary Vascular Disease

CLINICAL FINDINGS

This 50-year-old man was referred for evaluation of unexplained dyspnea. He had felt well until 1 year prior to evaluation, when he noted the insidious but progressive development of shortness of breath and easy fatigability. Six months prior to evaluation, he had an episode of acute severe substernal chest pain and dyspnea, which resulted in hospitalization and treatment for a suspected myocardial infarction. Following discharge from the hospital, he had lost 25 to 30 lb by watching his diet but remained somewhat dyspneic. He had no history of hypertension or diabetes mellitus. He had smoked three to four cigarettes daily until 2 years earlier. Physical examination was normal, with no signs of heart failure. Chest roentgenograms showed minimal pleural thickening bilaterally. Resting ECG showed normal QRS complexes and negative T waves in V_1 to V_3, suggesting right ventricular strain, but no Q waves.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer. He pedaled at 60 rpm without added load for 1 minute. The work rate was then increased 20 W per minute. Arterial blood was sampled every second minute, and intra-arterial blood pressure was recorded from a percutaneously placed brachial artery catheter. The patient stopped exercise because of overall fatigue and exhaustion; he denied having chest pain or dyspnea. There was a maximum of 0.5-mm ST-segment depression in leads II, V_5, and V_6 that disappeared at 3 minutes of recovery.

INTERPRETATION

Comments

The resting respiratory function studies showed normal lung mechanics but a significant reduction in diffusing capacity (Table 10.79.1). The ECG was suggestive of right ventricular strain.

Analysis

Referring to Flowchart 1 (Fig. 8.1), the peak $\dot{V}O_2$ was reduced, and the anaerobic threshold was borderline low (Table 10.79.2). Referring to Flowchart 4 (Fig. 8.4), the breathing reserve was normal, which leads to branch point 4.3. $\dot{V}E/\dot{V}CO_2$ at the *AT* was abnormally high (Fig. 10.79.1, panel 4), leading to the diagnosis of abnormal pulmonary circulation. The SaO_2 decreased during exercise (branch point 4.5), differentiating the diagnosis of primary pulmonary vascular disease from left ventricular failure. This conclusion is supported by the abnormally high V_D/V_T; $P(A-a)O_2$ and $P(a-ET)O_2$ (Table 10.79.3); steep heart rate–$\dot{V}O_2$ relationship; and low, relatively nonchanging O_2 pulse. Because these findings were highly suggestive of pulmonary vascular disease, a radionuclide ventilation–perfusion scan was performed, which demonstrated large unmatched perfusion defects, diagnostic of pulmonary thromboembolic disease.

Conclusion

This case is presented as an example of exercise testing, providing direction to the diagnostic evaluation of patients with dyspnea. The patient's treating physicians had attributed his acute symptoms to myocardial infarction, a diagnosis that was not well corroborated, and did not in itself explain his continued symptoms. Exercise findings directed testing to studies that established a diagnosis of chronic thromboembolic pulmonary vascular disease.

Table 10.79.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		50
Sex		Male
Height (cm)		185
Weight (kg)	86	92
Hematocrit (%)		46
VC (L)	5.10	4.68
IC (L)	3.40	2.94
TLC (L)	7.45	5.94
FEV_1 (L)	4.06	3.62
FEV_1/VC (%)	80	77
MVV (L/min)	161	152
D_{LCO} (mL/mm Hg/min)	32.3	21.2

Table 10.79.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	2.78	1.92
Maximum heart rate (beats/min)	170	164
Maximum O_2 pulse (mL/beat)	16.4	11.7
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.9
AT (L/min)	>1.25	1.25
Blood pressure (mm Hg [rest, max])		125/80, 161/92
Maximum $\dot{V}E$ (L/min)		104
Exercise breathing reserve (L/min)	>15	48
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	26.6	42.9
PaO_2 (mm Hg [rest, max ex])		83, 56
$P(A-a)O_2$ (mm Hg [rest, max ex])		26, 63
$PaCO_2$ (mm Hg [rest, max ex])		34, 33
$P(a-ET)CO_2$ (mm Hg [rest, max ex])		5, 9
V_D/V_T (rest, heavy ex)		0.40, 0.45
HCO_3^- (mEq/L [rest, 2-min recov])		22, 19

Table 10.79.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{V_D}{V_T}$
												ET	*a*	*(A − a)*	*ET*	*a*	*(a − ET)*			
0	Rest	125/80								7.41	21		73			34				
0.5	Rest		82	24	12.9	0.22	0.25	3.0	0.88			116			28			49	43	
1.0	Rest		82	22	14.7	0.28	0.35	4.3	0.80			112			29			46	37	
1.5	Rest		81	21	14.8	0.28	0.35	4.3	0.80			110			30			46	37	
2.0	Rest	119/83	81	16	12.0	0.23	0.29	3.6	0.79	7.42	22	112	83	26	29	34	5	46	37	0.40
2.5	Unloaded		94	23	26.8	0.56	0.66	7.0	0.85			109			30			44	38	
3.0	Unloaded	140/86	92	26	26.1	0.55	0.63	6.8	0.87	7.42	22	116	69	42	28	35	7	43	38	0.40
3.5	20		100	25	28.9	0.64	0.77	7.7	0.83			113			29			42	35	
4.0	20		100	22	32.8	0.72	0.86	8.6	0.84			115			28			43	36	
4.5	40		104	20	34.2	0.77	0.91	8.8	0.85			115			28			42	36	
5.0	40		108	22	37.1	0.84	0.99	9.2	0.85			115			28			42	36	
5.5	60		111	25	45.2	0.97	1.10	9.9	0.88			118			27			44	39	
6.0	60	146/86	115	25	47.2	1.02	1.16	10.1	0.88	7.42	22	116	64	47	28	35	7	44	39	0.42
6.5	80		121	27	52.5	1.16	1.31	10.8	0.89			116			28			43	38	
7.0	80		125	29	56.5	1.21	1.31	10.5	0.92			120			25			45	41	
7.5	100		132	27	60.8	1.32	1.41	10.7	0.94			120			26			44	41	
8.0	100	155/89	137	28	63.9	1.39	1.47	10.7	0.95	7.43	22	121	60	55	25	33	8	44	42	0.39
8.5	120		143	27	69.1	1.52	1.58	11.0	0.96			122			25			44	42	
9.0	120		147	28	72.8	1.62	1.66	11.3	0.98			123			25			43	42	
9.5	140		152	33	87.8	1.80	1.74	11.4	1.03			124			24			47	49	
10.0	140	161/92	156	31	89.7	1.88	1.79	11.5	1.05	7.40	20	124	58	60	24	33	9	46	49	0.42
10.5	160		160	34	94.8	1.97	1.88	11.8	1.05			125			24			47	49	
11.0	160	155/86	164	37	104.5	2.07	1.92	11.7	1.08	7.40	20	126	56	63	24	33	9	49	53	0.45
11.5	Recovery		144	29	85.2	1.86	1.80	12.5	1.03			123			25			44	46	
12.0	Recovery		127	27	73.4	1.62	1.52	12.0	1.07			122			26			44	47	
12.5	Recovery		116	23	54.5	1.23	1.14	9.8	1.08			122			27			43	46	
13.0	Recovery	152/86	109	20	35.7	0.84	0.72	7.2	1.06	7.37	19	119	73	45	30	34	4	40	43	0.36

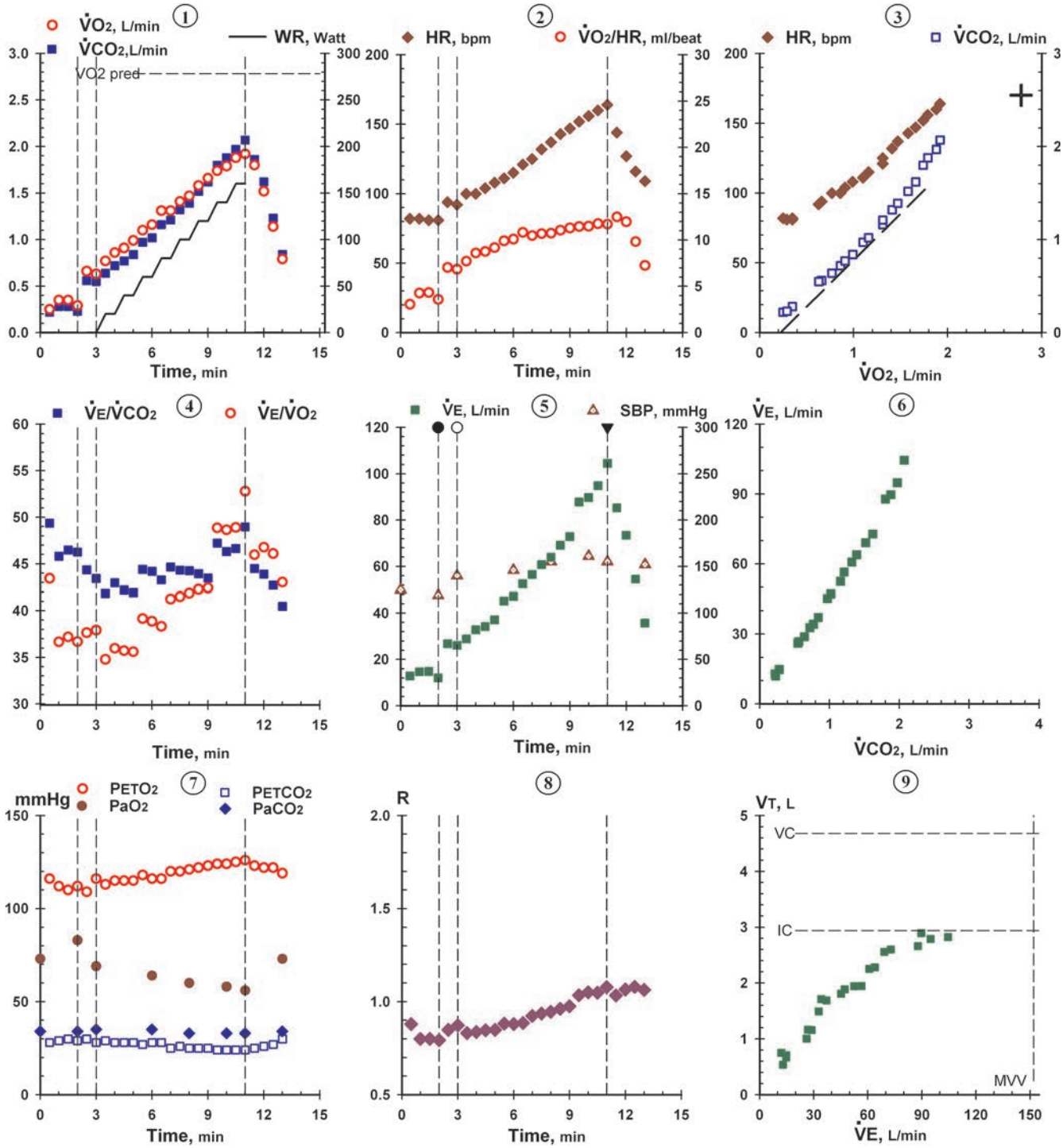

FIGURE 10.79.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 20 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $P_{ET}CO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Case 80 Evaluation of Unexplained Dyspnea: An Obese Woman at Risk for Pulmonary Hypertension

CLINICAL FINDINGS

This 49-year-old woman was referred for exercise testing to screen for possible pulmonary vascular disease. Her sister had a diagnosis of idiopathic pulmonary hypertension, and the patient herself had used anorexigens for weight control in the past. She reported chronic exercise intolerance, limited by dyspnea after walking several blocks on level terrain. Echocardiograms showed normal left ventricular function, but assessment of the right-sided chambers was limited by her obese body habitus. She was treated for obstructive sleep apnea with continuous positive airway pressure (CPAP) and for systemic hypertension with an angiotensin-converting enzyme (ACE) inhibitor and a diuretic. Physical exam was notable for obesity and mild peripheral edema. The ECG was normal.

EXERCISE FINDINGS

The patient performed exercise on a cycle ergometer beginning with 3 minutes of pedaling at 60 rpm without resistance, followed by continuous increase in work rate at a rate of 15 W per minute. She ended exercise with symptoms of leg fatigue. There were no significant ECG changes.

Comments

Resting pulmonary function tests demonstrated a mild ventilatory defect and spirometric findings typical of obesity. The DLCO was normal (Table 10.80.1).

Table 10.80.1

Selected Respiratory Function Data

Measurement	Predicted	Measured
Age (years)		49
Sex		Female
Height (cm)		164
Weight (kg)	64	124
VC (L)	3.25	2.85
IC (L)	2.17	2.82
ERV (L)	1.08	0.03
FEV_1 (L)	2.69	2.05
FEV_1/VC (%)	83	72
MVV (L/min)	99	87
DLCO (mL/mm Hg/min)	23.3	23.1

Analysis

The peak $\dot{V}O_2$ was within normal limits when compared to height-based predicted values, indicating normal cardiovascular capacity. The weight-indexed peak $\dot{V}O_2$ was low, however, indicating reduced capacity for ambulatory work (Table 10.80.2). Consistent with this, at the start of unloaded cycling exercise, $\dot{V}O_2$ increased to almost 1 L per minute, reflecting the exaggerated metabolic cost of lifting heavy legs (Fig. 10.80.1, panel 1). Subsequently, the increase in $\dot{V}O_2$ relative to work rate was normal. The anaerobic threshold was normal and heart rate increased normally relative to $\dot{V}O_2$ with attainment of a normal peak O_2 pulse. The patient may have developed CO_2 retention during exercise, which is common in severe obesity, as evidenced by an increase in P_{ETCO_2} early in the test (Table 10.80.3). Otherwise, the ventilatory responses were normal, including normal values for pulse oximetry and $\dot{V}E/\dot{V}CO_2$ @ *AT* and a large breathing reserve. The findings of normal cardiovascular capacity and pulmonary gas exchange were reassuring as they argue against the presence of hemodynamically significant pulmonary vascular disease. The test also provided an explanation for the patient's exertional dyspnea, which was attributable to the energetic cost of ambulatory work related to obesity, rather than cardiovascular dysfunction. These findings supported the decision to defer additional invasive diagnostic studies and provided a baseline against which to compare future measures.

Conclusion

This case demonstrates the effects of obesity on resting lung function and exercise gas exchange. It is presented as an illustration of how a normal exercise test can be useful in the evaluation of a patient with complaints of exertional dyspnea.

Table 10.80.2

Selected Exercise Data

Measurement	Predicted	Measured
Peak $\dot{V}O_2$ (L/min)	1.88	1.69
Peak $\dot{V}O_2$ (mL/min/kg)	29.4	13.6
Maximum heart rate (beats/min)	171	150
Maximum O_2 pulse (mL/beat)	11.0	11.3
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.3	8.9
AT (L/min)	> 0.94	1.12
Blood pressure (mm Hg [rest, max])		131/81, 237/99
Maximum $\dot{V}E$ (L/min)		46
Exercise breathing reserve (L/min)	>15	41
$\dot{V}E/\dot{V}CO_2$ @ *AT* or lowest	28.3	23.1

Table 10.80.3

Air Breathing

Time (min)	Work rate (W)	BP (mm Hg)	HR (min^{-1})	f (min^{-1})	$\dot{V}E$ (L/min BTPS)	$\dot{V}CO_2$ (L/min STPD)	$\dot{V}O_2$ (L/min STPD)	$\frac{\dot{V}O_2}{HR}$ (mL/beat)	R	pH	HCO_3^- (mEq/L)	P_{O_2}, mm Hg			P_{CO_2}, mm Hg			$\frac{\dot{V}E}{\dot{V}CO_2}$	$\frac{\dot{V}E}{\dot{V}O_2}$	$\frac{VD}{VT}$
												ET	*a*	(*A* − *a*)	*ET*	*a*	(*a* − *ET*)			
0																				
0.5	Rest	131/81	89	15	8.4	0.28	0.34	3.8	0.81			97			43			30	25	
1.0	Rest		91	15	8.9	0.30	0.36	4.0	0.83			99			42			30	25	
1.5	Rest		90	16	8.6	0.27	0.33	3.6	0.83			99			42			32	26	
2.0	Rest		96	20	10.6	0.32	0.38	4.0	0.84			100			41			33	27	
2.5	Rest		89	20	9.8	0.29	0.34	3.8	0.86			101			42			33	29	
3.0	Rest		88	17	9.7	0.32	0.35	4.0	0.90			102			41			31	28	
3.5	Unloaded	131/81	101	12	9.5	0.33	0.46	4.5	0.73			92			43			28	21	
4.0	Unloaded		107	27	17.8	0.60	0.71	6.6	0.85			98			42			30	25	
4.5	Unloaded		107	28	17.2	0.60	0.73	6.8	0.82			94			44			29	24	
5.0	Unloaded		108	22	15.8	0.61	0.76	7.1	0.80			89			47			26	21	
5.5	Unloaded		110	21	16.1	0.64	0.81	7.3	0.80			88			48			25	20	
6.0	Unloaded		113	22	17.5	0.71	0.88	7.8	0.80			87			49			25	20	
6.5	7		113	23	18.4	0.73	0.85	7.5	0.87			92			48			25	22	
7.0	15		116	23	18.5	0.76	0.89	7.7	0.85			90			49			24	21	
7.5	22		117	22	19.5	0.81	0.92	7.8	0.88			91			49			24	21	
8.0	30		120	24	22.2	0.91	1.01	8.5	0.89			93			48			25	22	
8.5	37		121	21	19.3	0.82	0.94	7.8	0.87			91			50			24	20	
9.0	45		122	20	19.9	0.87	1.03	8.5	0.84			88			51			23	19	
9.5	52		126	21	22.0	0.97	1.12	8.9	0.87			89			51			23	20	
10.0	60		127	25	25.0	1.07	1.19	9.4	0.90			91			50			23	21	
10.5	67		133	24	28.1	1.23	1.31	9.9	0.94			92			50			23	21	
11.0	75	237/99	135	28	30.5	1.31	1.33	9.8	0.99			95			50			23	23	
11.5	82		139	30	34.7	1.48	1.45	10.4	1.02			97			49			23	24	
12.0	90		141	31	39.2	1.63	1.48	10.5	1.10			102			47			24	26	
12.5	97		143	27	37.1	1.63	1.56	10.9	1.05			98			49			23	24	
13.0	105		150	29	43.3	1.87	1.69	11.3	1.11			101			49			23	26	
13.5	Recovery	237/99	149	28	45.8	1.90	1.62	10.8	1.17			104			47			24	28	
14.0	Recovery		137	24	37.7	1.58	1.17	8.5	1.35			109			47			24	32	
14.5	Recovery		133	26	34.4	1.34	0.89	6.7	1.51			113			45			26	39	
15.0	Recovery		127	22	27.7	1.01	0.66	5.2	1.54			117			42			27	42	
15.5	Recovery		126	23	22.0	0.78	0.52	4.1	1.50			117			42			28	42	

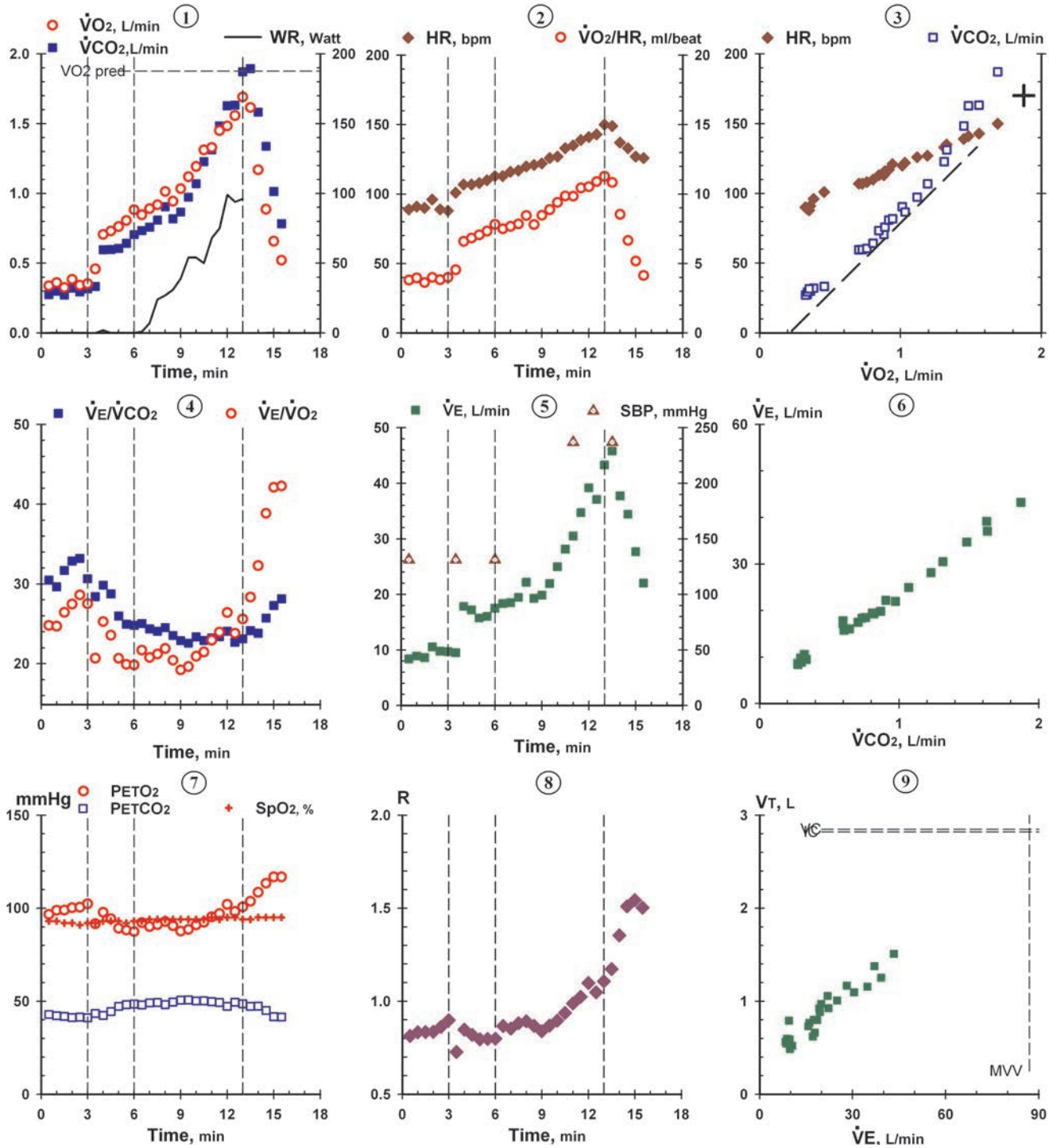

FIGURE 10.80.1. *Vertical dashed lines* in the panels in the left and middle columns indicate, from left to right, the beginning of unloaded cycling, start of increasing work rate at 15 W per minute, and start of recovery. In **panel 1**, the increase in work rate (right *y*-axis) is plotted with a scale of 100 W to 1 L of $\dot{V}O_2$ (left *y*-axis) such that work rate is plotted parallel to a $\dot{V}O_2$ slope of 10 mL/min/W. In **panel 3**, $\dot{V}CO_2$ (right *y*-axis) is plotted as a function of $\dot{V}O_2$ (*x*-axis) with identical scales so that the *diagonal dashed line* has a slope of 1 (45 degrees). $\dot{V}CO_2$ increasing more steeply than $\dot{V}O_2$ defines CO_2 derived from HCO_3^- buffer, as long as $\dot{V}E/\dot{V}CO_2$ (**panel 4**) is not increasing and $PETCO_2$ (**panel 7**) is not decreasing, simultaneously. The *black + symbol* in **panel 3** indicates predicted peak values of heart rate (left *y*-axis) and $\dot{V}O_2$ for the subject.

Appendix A

Symbols and Abbreviations

A bar above any symbol indicates a mean value.
A dot above any symbol indicates a time derivative.

Table A.1

Gases

Primary symbols		Examples	
V	Gas volume	V_A	Volume of alveolar gas
$\dot{V}$	Gas volume per unit time	$\dot{V}O_2$	Oxygen uptake per minute
P	Gas pressure	P_{AO_2}	Alveolar O_2 pressure
$\overline{P}$	Mean gas pressure	$\overline{P}_{CO_2}$	Mean capillary O_2 pressure
F	Fractional concentration of a gas	F_{IO_2}	Fractional concentration of O_2 in inspired gas
f	Respiratory frequency		
D	Diffusing capacity	D_{LCO}	Diffusing capacity of lung for carbon monoxide
R	Respiratory exchange ratio		
RQ	Respiratory quotient		
Q	Gas quantity		
$\dot{Q}$	Gas quantity per unit time (gas flow)	$\dot{Q}O_2$	Oxygen consumed per minute
STPD	Standard temperature and pressure (0°C, 760 mm Hg), dry		
BTPS	Body temperature and pressure, saturated with water vapor		

Secondary symbols		Examples	
I	Inspired gas	F_{IO_2}	Fractional concentration of O_2 in inspired gas
E	Expired gas	V_E	Volume of expired gas
A	Alveolar gas	$\dot{V}_A$	Alveolar ventilation per minute
ET	End tidal	P_{ETCO_2}	End-tidal CO_2 tension
T	Tidal gas	V_T	Tidal volume
D	Dead space gas	V_D	Physiological dead space volume
B	Barometric	P_B	Barometric pressure

Table A.2

Blood

Primary symbols		Examples	
$\dot{Q}$	Volume flow of blood per unit time	$\dot{Q}_C$	Blood flow through pulmonary capillaries per minute
C	Concentration of gas in blood phase	Ca_{O_2}	Content of O_2 in arterial blood
S	Percentage saturation of Hb with O_2	$S\bar{v}_{O_2}$	Saturation of Hb with O_2 in mixed venous blood
Secondary symbols		**Examples**	
a	Arterial blood	P_{ACO_2}	Partial pressure of CO_2 in arterial blood
v	Venous blood	$P\bar{v}_{O_2}$	Partial pressure of O_2 in mixed venous blood
c	Capillary blood	P_{cCO_2}	Partial pressure of CO_2 in pulmonary capillary blood

Table A.3

Lung Volumes and Flows

V_T	Tidal volume = Volume of air inhaled or exhaled with each breath
VC	Vital capacity = Maximal volume that can be expired after maximal inspiration
IC	Inspiratory capacity = Maximal volume that can be inspired from the resting end-expiratory level
ERV	Expiratory reserve volume = Maximal volume that can be expired from the resting end-expiratory level
FRC	Functional residual capacity = Volume of gas in lungs at end-expiration
RV	Residual volume = Volume of gas in lungs after maximal expiration
TLC	Total lung capacity = Volume of gas in lungs after maximal inspiration
FEV_x	Forced expired volume in *x* seconds (e.g., FEV_1 = forced expiratory volume in 1 second)
MVV	Maximal voluntary ventilation

Table A.4

Variables and Parameters

$\dot{V}_{O_2}$	Oxygen uptake	$\dot{V}_E/\dot{V}_{O_2}$	Ventilatory equivalent for O_2
$\dot{V}_{O_2}max$	Maximal aerobic power	$\dot{V}_E/\dot{V}_{CO_2}$	Ventilatory equivalent for CO_2
$\dot{V}_{CO_2}$	Carbon dioxide output	V_D/V_T	Physiological dead space–tidal volume ratio
$\dot{Q}_{O_2}$	Oxygen consumption	V_D	Physiological dead space
$\dot{Q}_{CO_2}$	CO_2 production	BR	Breathing reserve
AT	Anaerobic threshold	HR	Heart rate
LT	Lactate threshold	HRR	Heart rate reserve
LAT	Lactic acidosis threshold	WR	Work rate
R	Gas exchange ratio	$\Delta\dot{V}_{O_2}/\Delta WR$	Change in $\dot{V}_{O_2}$/change in WR
RQ	Respiratory quotient		

Appendix B

Glossary

Aerobic: Having molecular oxygen present; describes a metabolic process utilizing oxygen.

Alveolar to arterial P_{O_2} difference [$P(A - a)O_2$]: The difference between the ideal alveolar P_{O_2} (estimated) and the arterial P_{O_2}. A larger difference reflects an increase in the lungs' inefficiency with respect to oxygen exchange.

Alveolar ventilation ($\dot{V}_A$): The theoretic alveolar ventilation necessary to eliminate the metabolic CO_2 at the current arterial CO_2 tension. It assumes that $\dot{V}_A/\dot{Q}$ is uniform in all the acini so that their mean P_{CO_2} is equal to the arterial P_{CO_2}.

Anaerobic: Lacking or inadequate molecular oxygen; describes any metabolic process that does not use molecular oxygen.

Anaerobic threshold (*AT*): The exercise $\dot{V}_{O_2}$ above which anaerobic high-energy P_{O_4} production supplements aerobic high-energy P_{O_4} production, with the consequent lower redox state, increase in lactate-to-pyruvate (L/P) ratio, and net increase in lactate production at the site of anaerobiosis. Exercise above the AT is reflected by an increase in lactate concentration and L/P ratio in the muscle effluent and central blood, and a metabolic acidosis. Gas exchange is also affected by an increase in CO_2 output over that produced from aerobic metabolism, resulting from HCO_3^- buffering of lactic acid.

Analog-to-digital converter: A device for transforming continuously changing information into discrete units over some small time frame within which the value is considered to be relatively constant. This transforms continuous signals to a form that can be analyzed by a digital computer.

Arterial to end-tidal P_{CO_2} difference [$P(a - ET)\ CO_2$]: The difference between the mean arterial P_{CO_2} and the end-tidal P_{CO_2}. This is positive when the arterial P_{CO_2} is higher than the end-tidal P_{CO_2}. An increased positive difference generally reflects increased inefficiency of lung CO_2 exchange.

Arterial–mixed venous O_2 content difference [$C(a - \bar{v})O_2$]: The difference in the O_2 content of the arterial and venous blood, usually expressed in milliliters of O_2 per deciliter or liter of blood.

ATPS: A convention for expressing gas volume conditioned to the ambient (e.g., room) temperature and pressure, and saturated with water vapor at ambient temperature.

Breath-by-breath: The expression of a particular physiological value averaged over one entire respiratory cycle, usually expressed as the value that variable would have if maintained over an entire minute (e.g., ventilation expressed as L/min). Breath-by-breath is also used to describe a method for measurement of respiratory gas exchange in a breath during which respired gas volume and simultaneously measured expired gas concentration are integrated and reported.

Breathing reserve (BR): The difference between the maximum voluntary ventilation (measured at rest) and the maximum exercise minute ventilation. Hence, this represents the body's potential for further increasing ventilation at maximum exercise.

BTPS: A convention for expressing gas volume conditioned to body temperature and the ambient atmospheric pressure and fully saturated with water vapor at the subject's body temperature.

Carbon dioxide output ($\dot{V}_{CO_2}$): The amount of CO_2 exhaled from the body into the atmosphere per unit time, expressed in milliliters or liters per minute, STPD. This differs from CO_2 production rate under conditions in which additional CO_2 may be evolved from the body's stores ($\dot{V}_{CO_2}$ is higher than production rate) or CO_2 is added to the body's stores ($\dot{V}_{CO_2}$ is lower than production rate). In the steady state, CO_2 output equals CO_2 production rate. In rare circumstances, appreciable quantities of CO_2 can be eliminated from the body as bicarbonate via the gastrointestinal tract or by hemodialysis.

Carbon dioxide production ($\dot{Q}_{CO_2}$): The amount of carbon dioxide produced by the body's metabolic processes and, in some circumstances, released by buffering reactions within the body, expressed in milliliters or liters per minute, STPD.

Cardiac output ($\dot{Q}$): The flow of blood from the heart in a particular period, usually expressed as liters per minute. It is the product of the average stroke volume per beat and the heart rate (i.e., number of beats per minute).

Constant work rate test: An exercise test in which a constant power output is required of the subject.

Dead space or physiological dead space (V_D): The theoretic volume of gas taken into the lung that is not involved in gas exchange, assuming that the remaining volume (i.e., the alveolar volume) consists of acini having uniform $\dot{V}_A/\dot{Q}$ so that their mean P_{CO_2} equals the mean P_{CO_2} of the pulmonary capillary blood. The physiological dead space is made up of the anatomic dead space (the volume of the upper airways, trachea, and bronchi) and the alveolar dead space (the theoretical volume of alveoli that are ventilated but are unperfused).

Dead space–tidal volume ratio (V_D/V_T): The proportion of the tidal volume that is made up of the physiological dead space. This is an index of the relative inefficiency of pulmonary gas exchange to eliminate CO_2.

Diffusing capacity: A measure of the rate of uptake of a particular gas across the alveolar–capillary bed for a specified driving pressure for that gas. It is measured, therefore, as the volume of gas per unit time per pressure difference (e.g., mL/min/mm Hg). It is also referred to as the pulmonary gas transfer index (a term that more properly reflects the measurement). It is most practical to use carbon monoxide as the test gas for measurement of diffusing capacity of the lungs, in which case it is referred to as D_{LCO}.

Diffusion defect: A defect in the lungs' capacity for gas diffusion. This is typically caused either by an abnormally increased diffusion path length or by conditions in which the transit time of the red cell through the pulmonary capillary bed is so fast that insufficient time is available for complete diffusion equilibrium.

Disability: A legal term that considers the effect of a functional impairment on the patient's ability to perform a specific work task, along with other factors such as age, sex, education, social environment, job availability, and the energy requirements of the occupation.

End-tidal P_{CO_2} (P_{ETCO_2}): The P_{CO_2} of the respired gas determined at the end of a spontaneous exhalation. This is commonly the highest P_{CO_2} measured during the alveolar phase of the exhalation.

End-tidal P_{O_2} (P_{ETO_2}): The P_{O_2} determined in the respired gas at the end of a spontaneous exhalation. This is typically the lowest P_{O_2} determined during the alveolar portion of the exhalation.

Exponential: A process in which the instantaneous rate of change of a variable is proportional to the "distance" from a steady-state or required level; hence, the rate of change of the function under consideration is rapid when it is far from its steady-state value and slows progressively as the function approaches its steady state. If the process is known to be, or may be reasonably estimated to be, exponential, the time to reach 63% of the final value (i.e., to approach within 37% of the final value) is termed the time constant (τ) of the response. If the process is exponential, this time constant is related to the half time (the time to reach 50% of the final value) by the equation $t_{1/2} = 0.693 \times \tau$.

Fick method for cardiac output: A means of estimating cardiac output from the uptake of O_2 by the lungs and the arterial–mixed venous O_2 content difference. $\dot{Q} = \dot{V}_{O_2}/C(a - \bar{v})_{O_2}$. When the same principle is used to measure cardiac output with CO_2 as the test gas, the CO_2 output is divided by the $C(\bar{v} - a)_{CO_2}$.

Frequency response: This reflects the fidelity with which a measuring device can track rapidly changing physiologic information. The frequency response of the device is determined by applying rapidly changing signals of a particular amplitude, spanning a range of frequencies, and then establishing the frequency range over which the device tracks the signal at a predetermined level of accuracy.

Gas exchange ratio (R): The ratio of the carbon dioxide output to the oxygen uptake per unit time. This ratio reflects not only tissue metabolic exchange of the gases, but also the influence of transient change in gas storage of O_2, and especially of CO_2. For example, the gas exchange ratio exceeds the respiratory quotient during hyperventilation as additional CO_2 is evolved from the body's stores, whereas the gas exchange ratio is less than the respiratory quotient during transient hypoventilation when CO_2 is retained in the body's stores.

Half time ($t_{1/2}$): Unlike the time constant, which requires evidence of exponentiality for its determination, the half time of a response is a simple description of the time to reach half of the change to the final value, regardless of the function. It is, therefore, generally representative of the speed of approaching the steady state.

Heart rate reserve (HRR): The difference between the predicted highest heart rate attainable during maximum exercise and the actual highest heart rate, usually during exercise testing involving large muscle masses, such as during cycle or treadmill ergometry.

Ideal alveolar P_{O_2}: The hypothetical alveolar P_{O_2} that would be obtained if the lung were an ideal gas exchanger, that is, with ventilation uniformly matched to perfusion.

Impairment: A medical term reflecting a physiological abnormality. For exercise, it could represent any defect in the ventilatory-circulatory-metabolic coupling of external to internal respiration.

Incremental exercise test: An exercise test designed to provide a graded stress to the subject. The work rate required by the subject is usually increased over uniform periods, for example, every 4 minutes, every minute, every 15 seconds, or even continuously (e.g., ramp pattern increment).

Lactate: The anion of lactic acid.

Lactate threshold (*LT*): The exercise $\dot{V}_{O_2}$ above which a net increase in lactate production results in a sustained increase in central blood lactate concentration.

Lactic acid: A three-carbon carboxylic acid ($CH_3CHOHCOOH$) that is one of the potential end products of glucose oxidation. Another major product is pyruvic acid ($CH_3COCOOH$), which can undergo conversion to acetyl coenzyme A and can thereby be further oxidized. The relative amounts of lactic acid and pyruvic acid are determined by the cytosolic redox state; a low redox state, reflected by a high ratio of NADH to NAD^+, favors the generation of lactic acid, which, in turn, maintains the supply of NAD^+ necessary for glycolysis to continue. The presence of lactic acid is a marker of anaerobic metabolism.

Lactic acidosis threshold (*LAT*): The exercise $\dot{V}O_2$ above which arterial standard HCO_3^- decreases because of a net increase in lactate production. This can be detected by an increase in CO_2 output (from dissociation of H_2CO_3 as HCO_3^- buffers lactic acid) above that which would be predicted from aerobic metabolism alone during a progressively increasing work rate exercise test.

Laminar flow: A condition in which the flow of a fluid (gas or liquid) through a conduit is characterized by the uniform direction of flow of any plane sheet of the fluid, each of which flows parallel to any other in the direction of flow. Under conditions of laminar flow, the pressure difference between two fixed points upstream and downstream is directly proportional to flow and with the proportionality constant the resistance of the conduit.

Mass spectrometer: A device that separates and measures molecules of gas of a particular type in a mixed gas stream on the basis of their mass.

Maximum exercise heart rate: The highest obtainable heart rate during a maximum-effort test.

Maximum exercise ventilation: The highest minute ventilation achieved during a maximum–work rate test. This is usually determined by tests that tax large muscle masses, such as cycle or treadmill ergometry.

Maximum voluntary ventilation (MVV): The upper limit of the body's ability to ventilate the lungs. This is conventionally measured from maximal volitional effort for short periods (e.g., 12 seconds) and expressed in units of liters per minute, BTPS.

Mets: Mets, or metabolic equivalents, are the multiple of the resting metabolic rate expressed as O_2 uptake per minute per kilogram. The resting metabolic rate used in this calculation is usually 3.5 mL/min/kg, which is the average for a 40-year-old, 70-kg man. The weakness in applying this concept is that the exercise $\dot{V}O_2$ is usually not measured but assumed for a given treadmill grade and speed or cycle work rate. A further weakness is the assumption that the resting $\dot{V}O_2$ is 3.5 mL/min/kg for everyone.

Minute ventilation ($\dot{V}I$ or $\dot{V}E$): The volume of air taken into or exhaled from the body in 1 minute. This is conventionally expressed at body temperature, saturated with water at atmospheric pressure (BTPS).

Mixed venous blood: A sample of blood representative of the flow-weighted venous blood returning from all the organs of the body. Usually, blood obtained from the pulmonary artery is considered to be mixed venous blood.

Mixed venous O_2 or CO_2: The average partial pressure or gas content of the blood returning from all the tissues of the body and, having been fully mixed in the right heart, normally represented by the concentration or partial pressure of that substance in the pulmonary arterial blood.

Mixing chamber: A device that mixes the dead space and alveolar gas to produce a gas that is representative of the mixed expired gas. This is typically achieved by exhaling into a baffled chamber that mixes several breaths. The mixed expired concentration of a gas can be measured downstream from the chamber.

Oximeter: A device that uses light transmission or reflectance techniques to estimate the saturation of hemoglobin with oxygen. Direct oximetry is done on blood samples. For indirect oximetry, a site for measurement, such as the earlobe or finger, is selected because blood comes close to the skin and traverses the capillary bed with little loss of oxygen; hence, the mean capillary value will reflect arterial values. See ***Pulse oximeter***.

Oxygen consumption ($\dot{Q}O_2$): The amount of oxygen utilized by the body's metabolic processes in a given time, expressed in milliliters or liters per minute, STPD.

Oxygen content (CO_2): The volume of O_2 (STPD) in a given volume (L, dL, or mL) of blood. This includes the major component that is bound to hemoglobin and the amount physically dissolved in the blood.

Oxygen debt: The additional oxygen utilized in excess of the baseline needs of the body following a bout of exercise.

Oxygen deficit: The oxygen equivalent of the total energy utilized to perform the work that did not derive from reactions utilizing atmospheric oxygen taken into the body after the start of the exercise. Consequently, for moderate-intensity exercise, this O_2 deficit represents the energy equivalent of the depletion of the high-energy phosphate stores and oxygen stored in the body at the start of the work. For heavy or severe exercise, the oxygen deficit also includes the energy equivalent of the anaerobic processes.

Oxygen delivery: The amount of oxygen delivered to a tissue per unit time. It is, therefore, the product of the oxygen content of arterial blood and the blood flow to that tissue.

Oxygen pulse: The oxygen uptake divided by the heart rate. Hence, it is the amount of oxygen extracted by the tissues of the body from the O_2 carried in each stroke volume.

Oxygen uptake ($\dot{V}O_2$): The amount of oxygen extracted from the inspired gas in a given period, expressed in milliliters or liters per minute, STPD. This can differ from oxygen consumption under conditions in which oxygen is flowing into or being utilized from the body's stores. In the steady state, oxygen uptake equals oxygen consumption.

Phase I: The period following the onset of exercise that is required for the products of exercise metabolism to reach the lungs. During phase I, the mixed venous blood entering the pulmonary capillary bed has not changed its composition. Phase I is a result of the transit delay from the site of increased metabolism. Normally, this period is about 15 seconds.

Phase II: The period following the onset of exercise when the mixed venous blood gas concentrations continue to change because of changes in the effluent from the exercising muscles. Phase II reflects the "kinetic phase" of the gas exchange that begins at the end of phase I and continues until a steady state is obtained.

Phase III: The steady-state phase of gas exchange during exercise. For moderate exercise, it reflects the period in which the mixed venous gas concentrations have become constant. For heavy exercise, $\dot{V}O_2$ is observed to increase slowly during this phase, likely related to lactate metabolism.

Physiological dead space: See ***Dead space***.

Pneumotachograph: A device used to measure gas flow. It is typically composed of a screen across which the pressure drop stemming from the flow of gas may be measured. Flow may be integrated over time to yield the volume of air respired.

Power: See ***Work rate***.

Pulse oximeter: A noninvasive device for estimating arterial blood oxygen saturation using a combination of spectrophotometry and pulse plethysmography. The pulse oximeter probe is designed to be placed on the earlobe, finger tip, or forehead.

Pulse pressure: The difference between the systolic and the diastolic blood pressure.

Pump calibrator: A device that simulates the airflow and gas concentration waveforms encountered during respiration. Because the "metabolic rate" of such a device can be precisely calculated, it is useful for calibration of an exercise gas exchange measurement system.

R: See ***Gas exchange ratio***.

Ramp exercise test: An exercise testing protocol in which the work rate is continuously increased at a constant rate (e.g., 10 W/min). See ***Incremental exercise test***.

Response time: A means of characterizing the rate at which a device or system responds to a given signal. For example, in response to a sudden application of a constant level of input, how long does the output take to become constant? This can be characterized by the time constant, half time, or the time to reach 90% of the final value.

RQ (respiratory quotient): The ratio of the rate of carbon dioxide production to oxygen consumption. This ratio reflects the metabolic exchange of the gases in the body's tissues and is dictated by the percentage of substrate species (carbohydrates, fatty acids, and amino acids) used in energy production by the cells.

Set point: A term used in control system theory that reflects the particular value of a variable that the output of the system regulates. For example, a CO_2 set point is considered to be the operating level of arterial PCO_2, which is maintained at its relatively constant (i.e., set-point) value by changes in ventilation at a given level of CO_2 output.

Steady state: A characteristic of a physiologic system in which its functional demands are being met such that its output per unit time becomes constant. The time to achieve a steady state commonly differs for different physiologic systems. For example, following the onset of constant-load exercise, oxygen uptake rises to reach its steady state appreciably faster than CO_2 output or ventilation. A constant value attained by the system is not sufficient, however, to determine that the system is in a steady state. If the system reaches the limit of its output, and, as a result, its output becomes constant (as in the case of oxygen uptake reaching its maximum value), a steady state does not prevail. The system in this instance is in a limited state, not a steady state.

STPD: A convention for expressing gas volume at standard conditions of temperature and pressure, free of water vapor. The standard conditions are 0°C, 760 mm Hg, and dry gas.

Stroke volume: The volume of blood ejected from either ventricle of the heart in a single beat.

Sustainable work rate: A relative term that reflects the extent to which a particular work rate may be sustained for sufficient time for the successful completion of a particular occupational, recreational, or laboratory-induced work rate. Therefore, at a sustainable work rate, the subject does not fatigue within the time constraints of the requirements of the test.

Thermodilution blood flow measurement: A technique in which a measured bolus of physiologic fluid of known temperature, usually at 0°C, is injected into a vascular stream, such as in the right atrium, and the temperature of the blood is measured at a mixed downstream point, such as in the pulmonary artery. The addition of the cold bolus of fluid decreases the blood temperature at the downstream point; the amount of cooling is a function of the blood flow. Thermodilution cardiac output measurements are usually performed using a thermistor-tipped pulmonary artery catheter (Swan-Ganz type).

Tidal volume to inspiratory capacity ratio (VT/IC): The ratio of the volume of air exhaled during a breath (VT) to the volume potentially available for that

breath, the latter measured from the end-expiratory lung volume to the maximum inspiratory volume (IC). Hence, it reflects the proportion of the potential inspiratory volume excursion that is actually utilized for a particular breath.

Transcutaneous gas tension: A technique for estimating the partial pressure of the gas in the capillary blood perfusing a region of skin with high flow and low metabolic rate. When the intent of this measurement is to estimate arterial blood gases, it must be interpreted with caution, especially with rapid changes in arterial blood gases.

Transducer: A device that transforms energy from one form to another. Consequently, a pressure transducer is a device that changes fluid pressure into an electrical signal that can be analyzed and used for display or recording.

Turbulent flow: A condition in which the fluid (gas or liquid) flow has characteristic eddies, whorls, and diverse directional currents, such that additional energy needs to be applied to create a given fluid flow. Under conditions of turbulent flow, the relation between flow and pressure is nonlinear.

V-slope method: A method for determining the anaerobic or lactic acidosis threshold by plotting the volume of CO_2 output against the O_2 uptake on equal scales. The onset of lactic acidosis during an incremental exercise test is detected when CO_2 output increases relative to O_2 uptake, reflecting the increased CO_2 generated from bicarbonate as it buffers lactic acid.

$\Delta\dot{V}O_2(6-3)$: The difference in oxygen uptake between the sixth and the third minute of a constant-load exercise test. Normal subjects typically attain a steady state for constant-load exercise within 3 minutes during moderate exercise; hence, the $\Delta\dot{V}O_2$ (6 – 3) is zero. A positive value for this index reflects a degree of continuing non–steady state for the work and usually signals fatiguing exercise.

$\dot{V}O_2$max: The highest oxygen uptake obtainable for a given form of ergometry despite further work rate increases and effort by the subject. This is characterized by a plateau of oxygen uptake despite further increases in work rate.

$\Delta\dot{V}O_2/\Delta WR$: The increase in oxygen uptake in response to a simultaneous increase in work rate. Under appropriate conditions (e.g., steady-state aerobic work), this may be used to estimate the efficiency for muscular work.

Wasted ventilation ($\dot{V}D$): The difference between the computed alveolar ventilation and the measured minute ventilation. Also known as the physiological dead space ventilation, this term is meant to reflect the volume of the respired air that did not participate in alveolar capillary gas exchange; it is equal to $VD \times f$.

Work: A physical quantification of the force operating on a mass that causes it to change its location. Under conditions in which force is applied and no movement results (e.g., during an isometric contraction), no work is performed, despite increased metabolic energy expenditure. The unit of work is the joule ($kg\ m^2/sec^2$).

Work rate or power: This reflects the rate at which work is performed (i.e., work per unit time). Work rate is usually measured in watts ($kg\ m^2/sec^3$ or joule/sec) or in kilopond meters per minute (kp-m/min); 1 W is equivalent to 6.12 kp-m/min.

Appendix C

Calculations, Formulas, and Examples

This appendix presents the most essential formulas for calculating gas exchange and other related variables during exercise. An example accompanies the formula for each variable, using typical data acquired during exercise testing. Calculation of these variables uses well-defined and tested formulas, but several areas deserve particularly close attention. We address the specific problems of water vapor in the calculation of $\dot{V}O_2$, of making corrections for the dead space of the breathing valve, and of collecting data for breath-by-breath gas exchange analysis.

With computerized systems for collecting expired gas, measuring gas concentrations and ventilation, and calculating and displaying the relevant variables, some might be curious why one would need to understand how these calculations are made. It is important to understand how and how much variables can be affected by changes in the environment or by dysfunction of measurement devices. This understanding can be helpful in troubleshooting or deciding on the need to recalibrate the systems or obtain service for the equipment.

FORMULAS AND EXAMPLES OF GAS EXCHANGE CALCULATION

The formula for calculating each variable takes into account the condition under which each measurement is made and certain conventions. For the example calculations, we assume that expired gas is collected for exactly 2 minutes into a sealed meteorological balloon or Douglas bag. Assume that the gas volume is measured in a large spirometer or other suitable device, that fractional concentrations of O_2 and CO_2 are measured to within 0.04% using gas analyzers or a mass spectrometer, and that these are fractions of total gas volume excluding water vapor. An arterial blood sample is obtained during the collection of expired gas.

The measurements used for the example calculations are given in Table C.1.

Table C.1

Measurements Used for Example of Calculation of Gas Exchange

Measured volume: 54.2 L (ATPS)
Collection time: 2 minutes
Number of breaths: 41 in 2 minutes
Heart rate = 120/minute
Body temperature = 37°C
F_{IO_2} = 0.2093 (20.93%)
F_{ICO_2} = 0.0004 (0.04%)
F_{EO_2} = 0.162 (16.2%)
F_{ECO_2} = 0.041 (4.1%)
(Fractions of dry gas volume)
Hemoglobin = 15 g/100 mL
Valve dead space = 63 mL
Ambient temperature (T) = 22°C
Barometric pressure (P_B) = 760 mm Hg
Partial pressure of water, saturated gas at 22°C (P_{H_2O}) = 19 mm Hg
Pa_{O_2} = 91 mm Hg
Pa_{CO_2} = 36 mm Hg
pH = 7.44
Sa_{O_2} = 95%
P_{ETCO_2} = 38 mm Hg
$P\bar{v}_{O_2}$ = 27 mm Hg
$S\bar{v}_{O_2}$ = 50%

Minute Ventilation ($\dot{V}_E$)

The volume of gas exhaled divided by the time of collection in minutes is minute ventilation ($\dot{V}_E$). By convention, $\dot{V}_E$ is reported at body temperature saturated with water vapor at ambient pressure (BTPS), as in Equation 1. It may be necessary during calculation to obtain $\dot{V}_E$ at standard temperature and pressure (STPD) using Equation 2 or the appropriate tables (see Appendix E).

Most commonly, ventilation is measured at ambient temperature and the gas is fully saturated with water vapor at ambient temperature (ATPS). Equation 1 is used to adjust volume from ATPS to BTPS. The temperature and water vapor correction factors can also be found in Appendix E.

$$\dot{V}_E\ (\text{L/min, BTPS}) = \dot{V}_E\ (\text{L/min, ATPS}) \times \frac{(273 + 37)}{273 + T} \times \frac{P_B - P_{H_2O}\ (\text{at } T)}{P_B - 47} \quad (1)$$

where T is ambient temperature (°C), body temperature is 37°C, P_{H_2O} at 37°C is 47 mm Hg (fully saturated), and P_B is barometric pressure.

Alternatively, ventilation can be measured at STPD. From $\dot{V}_E$ (BTPS), $\dot{V}_E$ (STPD) can be obtained using Equation 2, which converts BTPS to STPD (at 273°K, barometric pressure = 760 mm Hg, and no water vapor present) for $\dot{V}_{CO_2}$ and $\dot{V}_{CO_2}$ calculations.

$$\dot{V}_E\ (\text{L/min, STPD}) = \dot{V}_E\ (\text{L/min, BTPS}) \times \frac{273}{(273 + 37)} \times \frac{P_B - 47}{760}$$

which becomes

$$\dot{V}_E\ (\text{L/min, STPD}) = \dot{V}_E\ (\text{L/min, BTPS}) \times 0.826 \quad (2)$$

if P_B = 760 mm Hg.

Example

$$\dot{V}_E\ (\text{L/min, ATPS}) = \frac{\text{Total volume (ATPS)}}{\text{Total collection time}} = 54.2/2\ \text{min} = 27.1$$

Then, from Equation 1,

$$\dot{V}_E\ (\text{L/min, BTPS}) = 27.1 \times \frac{310}{(273 + 22)} \times \frac{(760 - 19)}{(760 - 47)} = 29.6$$

and, from Equation 2,

$$\dot{V}_E\ (\text{L/min, STPD}) = 29.6 \times 0.826 = 24.3$$

Respiratory Frequency (f)

$$f\ (\text{min}^{-1}) = \frac{\text{Number of complete breaths}}{\text{Total time for complete breaths}} \quad (3)$$

Example

$$f\ (\text{min}^{-1}) = \frac{41\ \text{breaths}}{2\ \text{min}} = 20.5$$

Tidal Volume (V_T)

$$V_T\ (\text{L, BTPS}) = \frac{\dot{V}_E\ (\text{L/min, BTPS})}{f} \quad (4)$$

Example

$$V_T\ (\text{L, BTPS}) = \frac{29.6}{20.5} = 1.44$$

Carbon Dioxide Output ($\dot{V}_{CO_2}$)

The CO_2 output and O_2 uptake are reported, by convention, under STPD conditions. If $\dot{V}_E$ and $\dot{V}_I$ are measured at or converted to STPD conditions, F_{ECO_2} is the fraction of dry gas volume, and F_{ICO_2} is zero or negligible, then

$$\dot{V}_{CO_2}\ (\text{L/min, STPD}) = \dot{V}_E\ (\text{L/min, STPD}) \times F_{ECO_2} \quad (5)$$

or, for P_B = 760 mm Hg,

$$\dot{V}_{CO_2}\ (\text{L/min, STPD}) = \dot{V}_E\ (\text{L/min, BTPS}) \times 0.826 \times F_{ECO_2} \quad (6)$$

Example

Substituting $\dot{V}_E$ and F_{ECO_2} (Table C.1) into Equation 5,

$$\dot{V}_{CO_2}\ (\text{L/min, STPD}) = 24.3 \times 0.041 = 0.997$$

Oxygen Uptake ($\dot{V}_{O_2}$)

For the derivation of the formula for $\dot{V}_{O_2}$ and consideration of water vapor, see "Special Considerations for Calculation of Gas Exchange Variables" later in this appendix. Equation 7 should be used only for expired gas containing no water vapor (or measured as such).

If $\dot{V}_E$ is measured at or converted to STPD, F_{IO_2} is 0.2093 (dry room air), F_{ECO_2} and F_{EO_2} are fractions of CO_2 and O_2 in dry gas, respectively, and F_{ICO_2} is 0, then

$$\dot{V}_{O_2}\ (\text{L/min, STPD}) = \dot{V}_E\ (\text{L/min, STPD}) \times (\Delta F_{O_2})\text{true, dry} \quad (7)$$

where (ΔF_{O_2})true, dry = 0.265 − 1.265 × F_{EO_2} − 0.265 × F_{ECO_2} for a person breathing room air. The (ΔF_{O_2})true, dry can also be obtained from the nomogram in Appendix E.

Example

Substituting from Table C.1 into Equation 7:

$$(\Delta F_{O_2})\text{true, dry} = 0.265 - 0.205 - 0.0108 = 0.049$$

$$\dot{V}_{O_2}\ (\text{L/min, STPD}) = 24.3 \times 0.049 = 1.19$$

Gas Exchange Ratio (R)

$$R = \frac{\dot{V}CO_2\ (L, min\ STPD)}{\dot{V}O_2\ (L, min\ STPD)} \quad (8)$$

Example

$$R = \frac{0.997}{1.19} = 0.84$$

Ventilatory Equivalents for Carbon Dioxide and Oxygen ($\dot{V}E/\dot{V}CO_2$, $\dot{V}E/\dot{V}O_2$)

The ventilatory equivalents for CO_2 and O_2 are measurements of the ventilatory requirement for that metabolic rate. By convention, they are expressed as $\dot{V}E$ (L/min, BTPS) divided by $\dot{V}CO_2$ or $\dot{V}O_2$ (L/min, STPD). Because the portion of the ventilation wasted in clearing the breathing valve dead space is disregarded in determining the ventilatory requirement, the product of valve dead space (VD_m) and respiratory frequency (f) is subtracted from the total $\dot{V}E$:

$$\dot{V}E/\dot{V}CO_2 = \frac{\dot{V}E\ (L/min, BTPS - [f\ min^{-1} \times VD_m\ (L)])}{\dot{V}CO_2\ (L/min, STPD)} \quad (9)$$

$$\dot{V}E/\dot{V}O_2 = \frac{\dot{V}E\ (L/min, BTPS - [f\ min^{-1} \times VD_m\ (L)])}{\dot{V}O_2\ (L/min, STPD)} \quad (10)$$

Example

$$\dot{V}E/\dot{V}CO_2 = \frac{29.6 - [20.5 \times 0.064]}{0.997} = 28.4$$

$$\dot{V}E/\dot{V}O_2 = \frac{29.6 - [20.5 \times 0.064]}{1.19} = 23.8$$

Oxygen Pulse ($\dot{V}O_2/HR$)

$\dot{V}O_2/HR$ (mL, STPD/beat)

$$= \frac{\dot{V}O_2\ (L/min, STPD) \times 1000\ mL/L}{HR\ (beats/min)} \quad (11)$$

Example

$$\dot{V}O_2/HR\ (mL, STPD/beat) = \frac{1.19 \times 1000}{120} = 9.9$$

Alveolar P_{O_2} (P_{AO_2})

P_{AO_2} (mm Hg)

$$= F_{IO_2} \times (P_B - 47) - \frac{P_{ACO_2}}{R}[1 - F_{IO_2}(1 - R)] \quad (12)$$

where barometric pressure is in mm Hg, P_{ACO_2} is ideal alveolar P_{CO_2} in mm Hg, R is the gas exchange ratio, and F_{IO_2} is the fraction of inspired O_2, dry. Usually, the assumption that $P_{ACO_2} = P_{aCO_2}$ is used, and the term $F_{IO_2} \times (1 - R)$ may be dropped because it is so small that it has an insignificant effect on the calculated P_{AO_2}, especially during air breathing. This simplifies the formula to the following:

$$P_{AO_2}\ (mm\ Hg) = F_{IO_2} \times (P_B - 47) - \frac{P_{ACO_2}}{R} \quad (13)$$

Whereas R in the fasting state is often assumed to be 0.8 at rest, R should always be calculated during exercise because it may range from 0.7 to 1.4 or more, which will have an appreciable effect on alveolar P_{O_2} calculation.

Example

Substituting into Equation 13,

$$P_{AO_2}\ (mm\ Hg) = (0.2093 \times 713) - \frac{36}{0.84} = 106$$

Alveolar–Arterial P_{O_2} Difference [$P(A-a)O_2$]

$$P(A-a)O_2\ (mm\ Hg) = P_{AO_2} - P_{aO_2} \quad (14)$$

where P_{AO_2} is determined as above and P_{aO_2} is arterial P_{O_2}.

Example

$$P(A-a)O_2\ (mm\ Hg) = 106 - 91 = 15$$

Arterial End-Tidal P_{CO_2} Difference [$P(a-ET)CO_2$]

$$P(a-ET)CO_2 = P_{aCO_2} - P_{ETCO_2} \quad (15)$$

where P_{aCO_2} is arterial P_{CO_2} and P_{ETCO_2} is end-tidal P_{CO_2}.

Example

$$P(a-ET)CO_2 = 36 - 38 = -2\ mm\ Hg$$

Physiological Dead Space (V_D)

$$V_D\ (L) = V_T\ (L) \times \frac{(P_{aCO_2} - P\bar{E}CO_2)}{P_{aCO_2}} - VD_m\ (L) \quad (16)$$

where V_T is tidal volume, P_{aCO_2} is arterial P_{CO_2}, $P\bar{E}CO_2$ is mixed expired P_{CO_2}, and VD_m is breathing valve dead space. Mixed expired P_{CO_2} can be calculated as follows:

$$P\bar{E}CO_2 = \frac{\dot{V}CO_2\ (L/min, STPD)}{\dot{V}E\ (L/min, STPD)} \times (P_B - 47\ mm\ Hg)$$

Example

$$P\bar{E}CO_2 = \frac{0.997}{24.3} \times 713 = 29$$

$$V_D\ (L) = 1.44 \times \frac{36 - 29}{36} - 0.064 = 0.22$$

Physiological Dead Space–Tidal Volume Ratio (V_D/V_T)

$$\frac{V_D}{V_T} = \frac{(Pa_{CO_2} - P\bar{E}_{CO_2})}{Pa_{CO_2}} - \frac{V_{D_m}(L)}{[V_T\ (L) - V_{D_m}(L)]} \qquad (17)$$

Example

$$\frac{V_D}{V_T} = \frac{39 - 29}{36} - \frac{0.064}{1.44} = 0.15$$

V_D/V_T must be calculated using the arterial P_{CO_2}. There has been an unfortunate trend of calculating V_D/V_T "noninvasively" during exercise by substituting P_{ETCO_2} for Pa_{CO_2} in the foregoing formulas, or by estimating Pa_{CO_2} from P_{ETCO_2} using a regression formula derived from normal subjects. As shown in Chapters 3 and 4, P_{ETCO_2} and Pa_{CO_2} are nearly equal only in normal subjects at rest. During exercise, the $P(a-ET)CO_2$ becomes negative in normal subjects, whereas it becomes larger and more positive in patients with lung disease who have increased V_D/V_T. Therefore, the relation between Pa_{CO_2} and P_{ETCO_2} during exercise ranges widely and unpredictably.[1] Furthermore, even small errors in Pa_{CO_2} may result in clinically important differences in the calculated V_D/V_T.

Cardiac Output

The cardiac output ($\dot{Q}$) can be determined by thermal indicator dilution or by the Fick method using $\dot{V}_{O_2}$ and arterial–mixed venous O_2 content difference:

$$\dot{Q}\ (L/min) = \frac{\dot{V}_{O_2}\ (mL/min,\ STPD)}{(Ca_{O_2} - C\bar{v}_{O_2})\ (mL\ O_2/L\ blood)} \qquad (18)$$

where Ca_{O_2} is O_2 content in arterial blood and $C\bar{v}_{O_2}$ is O_2 content in mixed venous blood. These can be calculated as follows:

$$C_{O_2}\ (mL\ O_2/100\ mL) = (S_{O_2} \times 0.01 \times 1.34\ mL\ O_2/g\ Hb \times [Hb]) + (0.003\ mL\ O_2/mm\ Hg/100\ mL \times P_{O_2}) \qquad (19)$$

where [Hb] is hemoglobin concentration in g/100 mL blood and S_{O_2} is the percentage of oxyhemoglobin saturation. Note that this calculation gives O_2 content in mL O_2/100 mL of blood and is converted to mL O_2/L blood by multiplying by 10.

Example

Ca_{O_2}(mL O_2/100 mL)
$= (95\% \times 0.01 \times 1.34 \times 15) + (0.003 \times 91) = 19.4$

$C\bar{v}_{O_2}$ (mL O_2/100 mL)
$= (50\% \times 0.01 \times 1.34 \times 15) + (0.003 \times 27) = 10.1$

$(Ca_{O_2} - C\bar{v}_{O_2})$
$= 19.4 - 10.1 = 9.3$ mL O_2/100 mL $= 93$ mL O_2/L

$$\dot{Q}\ (L/min) = \frac{1190\ (mL/min,\ STPD)}{93\ mL\ O_2/L\ blood} = 12.8$$

A noninvasive determination of cardiac output has been described using an analogous formula for CO_2 and an estimate of mixed venous CO_2 content (indirect Fick method) from a single-exhalation method[2] or a rebreathing method.[3] With the rebreathing method, as a mixture of CO_2 and high inspired O_2 is rebreathed, the P_{CO_2} of the rebreathed gas rapidly approaches that of mixed venous blood. This value is then referred to a CO_2 dissociation curve to determine CO_2 content. However, as shown in Chapter 3, estimating mixed venous CO_2 content ($C\bar{v}_{CO_2}$) has great pitfalls during exercise.

Sun et al.,[4,5] using direct measurements of blood gases and pH, addressed the problem of indirectly determining CO_2 contents in arterial and mixed venous blood. pH profoundly affects the CO_2 dissociation curve, making it impossible to get a reasonably reliable estimate of C_{CO_2}, particularly for $C\bar{v}_{CO_2}$. This study showed that $C\bar{v}_{CO_2}$ did not increase in proportion to $P\bar{v}_{CO_2}$ during exercise. In fact, $C\bar{v}_{CO_2}$ actually decreased as $P\bar{v}_{CO_2}$ increased above the anaerobic threshold because of the shift downward of the CO_2 dissociation curve as pH decreased. Also, as discussed in reference to calculating V_D/V_T, it is invalid to derive Pa_{CO_2} and Ca_{CO_2} from P_{ETCO_2} because the difference between these two measures of P_{CO_2} is variable, particularly in patients, and is too large to obtain reliable estimates of CO_2 content with the precision required for valid measurements.

Using direct measures of arterial and mixed venous O_2 and CO_2 gas tensions, pH, and hemoglobin concentrations, Sun et al.[4,5] compared the O_2 and CO_2 values determined by direct Fick cardiac output measurements during exercise from rest to peak $\dot{V}_{O_2}$. They found that the two test gases gave the same results, but the variability was greater with CO_2. The reader is referred to the two papers by Sun et al.[4,5] on this topic, where the problems of measuring cardiac output by the indirect Fick method are thoroughly discussed.

CALCULATIONS AT MAXIMUM EXERCISE

Breathing Reserve (BR)

$$BR\ (L/min) = MVV\ (L/min) - \dot{V}_E\ (L/min)\ \text{at maximum exercise} \qquad (20)$$

$$BR\ (\%) = \frac{MVV\ (L/min) - \dot{V}_E\ (L/min)\ \text{at maximum exercise}}{MVV\ (L/min)} \times 100 \qquad (21)$$

where MVV is maximum voluntary ventilation at rest.

Example

If MVV is 82 L/min and $\dot{V}_E$ at maximum exercise is 65 L/min, then

$$BR\ (L/min) = 82 - 65 = 17\ L/min$$

$$BR\ (\%) = \frac{82 - 65}{82} \times 100 = 21\%$$

Heart Rate Reserve (HRR)

$$\text{HRR (beats/min)} = \text{Predicted maximum HR} - \text{HR at maximum exercise} \quad (22)$$

$$\text{HRR (\%)} = \frac{\text{Predicted maximum HR} - \text{HR at maximum exercise}}{\text{Predicted maximum HR}} \times 100 \quad (23)$$

where predicted maximum HR (adults) = 220 − age (years).

Example

For a 60-year-old man, predicted maximum HR = 220 − 60 = 160 beats/min. If HR at maximum exercise is 145 beats/min, then

$$\text{HRR (beats/min)} = 160 - 145 = 15$$

$$\text{HRR (\%)} = \frac{160 - 145}{160} \times 100 = 9\%$$

SPECIAL CONSIDERATIONS FOR CALCULATION OF GAS EXCHANGE VARIABLES

Water Vapor and Oxygen Uptake

Oxygen uptake ($\dot{V}O_2$) is determined most often by collection and analysis of expired gas. The usual calculation method determines $\dot{V}O_2$ from expired ventilation, expired CO_2 fraction, and expired O_2 fraction, and is based on the assumption that the inspired and expired volumes of nitrogen (and other inert gases) do not differ during the collection period. During rest and exercise, this method has been found to be satisfactory.[6,7] Nevertheless, errors may be introduced if careful attention is not paid to methods and calculations. This is especially true of how water vapor is handled because this variable can greatly affect the calculation of $\dot{V}O_2$.

If the Scholander or Haldane method of gas analysis or a mass spectrometer is used, or water vapor is removed by drying the gas prior to measurement, then measured gas concentration is relative to total gas minus the volume of water vapor. Thus, the dilution of the concentration of each gas caused by water vapor can be ignored and calculations are relatively simple:

$$\dot{V}O_2\ (\text{L/min, STPD}) = [F_{IO_2} \times \dot{V}I\ (\text{L/min, STPD})] - [F_{EO_2} \times \dot{V}E\ (\text{L/min, STPD})]$$

where F_{IO_2} and F_{EO_2} are the O_2 fractions of dry gas volumes. If, over the period of collection, the volumes of inspired and expired nitrogen (and other inert gases) are equal during breathing, then

$$\dot{V}I \times F_{IN_2} = \dot{V}E \times F_{EN_2}$$

and

$$\dot{V}I = (F_{EN_2}/F_{IN_2}) \times \dot{V}E$$

where F_{IN_2} and F_{EN_2} are the fractional concentrations of nitrogen and other inert gases.

Because $(F_{IN_2} + F_{IO_2} + F_{ICO_2}) = 1$ and $(F_{EN_2} + F_{EO_2} + F_{ECO_2}) = 1$, then

$$\dot{V}I = \frac{(1 - F_{EO_2} - F_{ECO_2})}{(1 - F_{IO_2} - F_{ICO_2})} \times \dot{V}E$$

and

$$\dot{V}O_2\ (\text{L/min, STPD}) = \left[\frac{F_{IO_2} \times (1 - F_{EO_2} - F_{ECO_2})}{(1 - F_{IO_2} - F_{ICO_2})}\right] \times \dot{V}E\ (\text{L/min, STPD}) \quad (24)$$

The quantity in brackets is called the true O_2 difference, (ΔF_{O_2})true.

If we assume that $F_{ICO_2} = 0$, or is negligible, then

$$(\Delta F_{O_2})\text{true} = \frac{(F_{IO_2} - F_{EO_2} - F_{IO_2} \times F_{ECO_2})}{(1 - F_{IO_2})}$$

and

$$\dot{V}O_2\ (\text{L/min, STPD}) = \dot{V}E\ (\text{L/min, STPD}) \times (\Delta F_{O_2})\text{true}$$

For room-air inspired gas, F_{IO_2} (dry) = 0.2093, and

$$\dot{V}O_2\ (\text{L/min, STPD}) = \dot{V}E\ (\text{L/min, STPD}) \times (0.265 - 1.265 \times F_{EO_2} - 0.265 \times F_{ECO_2}) \quad (25)$$

If water vapor is not removed from the gas and the method of gas analysis measures gas fraction of the total gas volume including water vapor, as is the case for most discrete O_2 analyzers, then the water vapor will reduce each dry gas fraction by the following factor:

$$\frac{(P_B - P_{H_2O})}{P_B} \text{ or } (1 - F_{H_2O})$$

In this case, the determination of $\dot{V}O_2$ is affected by water vapor as follows. First, $\dot{V}O_2$ can be expressed using $\dot{V}I$ and $\dot{V}E$ determined under the conditions of measurement (i.e., at temperature T and containing some water vapor):

$$\dot{V}O_2\ (\text{L/min, STPD}) = \frac{273}{273 + T} \times \frac{P_B}{760} \times (\dot{V}I \times F_{IO_2} - \dot{V}E \times F_{EO_2}) \quad (26)$$

where $\dot{V}I$ and $\dot{V}E$ are L/min at temperature T, and F_{IO_2} and F_{EO_2} are fractions of $\dot{V}I$ and $\dot{V}E$, respectively, including the volume of water vapor.

Because $\dot{V}I = (F_{EN_2}/F_{IN_2}) \times \dot{V}E$, and $(F_{EN_2} + F_{EO_2} + F_{ECO_2} + F_{EH_2O}) = 1$ and $(F_{IN_2} + F_{IO_2} + F_{ICO_2} + F_{IH_2O}) = 1$, then substituting into Equation 26 gives

$$\dot{V}O_2\ (\text{L/min, STPD}) = \dot{V}E\ (\text{L/min at } T) \times k\ (T, P_{H_2O}) \times (\Delta F_{O_2})\text{true} \quad (27)$$

where

$$k\,(T, P_{H_2O}) = \frac{273}{273 + T} \times \frac{P_B}{760}$$

and

$$(\Delta F_{O_2})\text{true} = \frac{F_{IO_2} \times (1 - F_{ECO_2} - F_{EH_2O}) - F_{EO_2} \times (1 - F_{IH_2O})}{(1 - F_{IO_2} - F_{IH_2O})}$$

The calculation of $\dot{V}O_2$ is simpler if the expired gas is dried prior to analysis for O_2 and CO_2. However, Beaver[8] provides a nomogram for calculation of oxygen uptake in the presence of water vapor that can be used to determine $\dot{V}O_2$ and R from a sample of mixed expired gas assumed to be fully saturated with water vapor at a known temperature (see Appendix E). The subject is assumed to be breathing room air, and the O_2 and CO_2 analyzers display the fractions of total expired gas including water vapor. Substantial errors would result if water vapor were not taken into account. Again, the correction is not needed when gas fractions are measured as fractions of dry gas.

Breath-by-breath measurement systems must deal with the effect of water vapor on calculation of $\dot{V}O_2$. Rapidly responding gas analyzers or a respiratory mass spectrometer is used. A mass spectrometer may be adjusted to "ignore" water vapor if the sum of ion voltages is made up of only those measuring N_2, O_2, CO_2, and argon, with water vapor ignored in both inspired and expired gases. If this method is used, then the volume to be multiplied by true O_2 fraction should be adjusted to the dry volume.

Rapidly responding O_2 analyzers and infrared CO_2 analyzers used without drying the analyzed gas read fractions of total gas volume and therefore read lower concentrations than if the same gas were measured after being dried. As shown in Equation 27, the values can be used in a breath-by-breath system if F_{EH_2O} and F_{IH_2O} are known.[9] The assumption that expired gas is fully saturated at some known temperature is the starting point for several approaches to dealing with this in breath-by-breath systems.

First, the expired gas sample can be kept warm to prevent condensation. If gas is fully saturated at a known temperature, F_{EH_2O} can be estimated. A heated sampling tube is necessary, and the temperature must be accurately known. For example, assuming a value of 37°C when actual expired gas temperature is 32°C can result in a 7% to 8% error in $\dot{V}O_2$. During exercise, expired gas rapidly cools in the mouthpiece and breathing valve to as low as 32°C. Because gas for analysis is most often sampled at this location in breath-by-breath systems, then even if the gas is rewarmed, there will have been some unknown loss of water vapor to condensation. A second approach is to allow the sampled gas to cool to a known temperature. This avoids the problem of indeterminate loss of water vapor from cooling followed by rewarming.

Another approach used by many exercise systems employs conducting tubing that allows water vapor to pass out of the gas being conveyed to the gas analyzer until water vapor equilibrium is reached with the atmosphere. Thus, water vapor partial pressure in the gas analyzers is equal to the ambient P_{H_2O} rather than saturated at some imprecisely known temperature. This method avoids the need to know the precise temperature of the respired gas and does not adversely affect the response time.

Oxygen Uptake and Oxygen Breathing

The foregoing calculation of $\dot{V}O_2$ is intended for measurement during room-air breathing. The use of the same equations during breathing of oxygen-enriched inspired gas mixtures has several potential problems. The relation of $\dot{V}I$ to $\dot{V}E$ is sensitive to small measurement errors when F_{IO_2} and F_{EO_2} are high and F_{IN_2} and F_{EN_2} are low. In addition, the assumption that $\dot{V}I \times F_{IN_2} = \dot{V}E \times F_{EN_2}$ is not valid during the transient wash-out period during which hyperoxic gas is inspired and more nitrogen is removed during expiration than is added during inspiration. Finally, if the subject is breathing 100% oxygen, the equations given previously cannot be used at all because there is no inspired or expired nitrogen.

Although calculation of $\dot{V}O_2$ during enriched oxygen breathing is theoretically possible, the accuracy of $\dot{V}O_2$ using conventional equations and measurements is almost certainly less than when the subject is breathing room air. $\dot{V}O_2$ calculated with F_{IO_2} greater than 0.21 should be interpreted with caution. Some investigators have demonstrated that accurate determination of $\dot{V}O_2$ can be achieved with F_{IO_2} up to 0.30 to 0.50.

An alternative approach to testing subjects during oxygen breathing is to ignore or not make measurements of $\dot{V}O_2$. Often, a reason for exercise testing is to determine the need for supplemental oxygen in a particular patient. This question can usually be answered by comparison of maximum work rate, heart rate, respiratory frequency, minute ventilation, $\dot{V}E/\dot{V}CO_2$, and exercise endurance between a maximum exercise test on room air with a similar test during oxygen breathing. An objective improvement in exercise capacity and decreased $\dot{V}E$ and $\dot{V}E/\dot{V}CO_2$ are encouraging signs of a beneficial effect of supplemental O_2.

Valve Dead Space and Physiological Dead Space

The physiological dead space consists of the anatomic dead space and the alveolar dead space. During measurement, the volumes of the breathing valve and mouthpiece apparatus are considered to be in series with the anatomic dead space. This apparatus dead space is

usually subtracted from the V_D calculated by the Engoff modification of the Bohr equation:

$$V_D = V_T\ (L) \times \frac{Pa\overline{CO}_2 - P\overline{E}CO_2}{Pa\overline{CO}_2} - V_{D_m}\ (L)$$

where V_D is subject dead space, V_T is tidal volume, and V_{D_m} is the volume of the apparatus (or valve dead space).

Bradley and Younes,[10] Suwa and Bendixen,[11] and Singleton et al.[12] reported that the effective dead space of the valve (the correction term V_{D_m}) may be different from the measured mechanical dead space. The readers are referred to their thorough analyses of the proper correction value under various conditions.

In practice, most reports of V_D during exercise have corrected for apparatus dead space by subtracting the entire mechanical dead space. Any potential error can be minimized if the valve dead space is small and the subject's tidal volume is relatively large compared with V_{D_m}. Valves with large dead spaces may be necessary, however, because they usually offer smaller breathing resistances at high inspiratory and expiratory flows. These high flows would be encountered when studying healthy normal subjects with large tidal volumes during exercise. On the other hand, patients with small tidal volumes will usually not generate high flows during exercise, and the valves with small dead spaces are recommended.

Calculations for Breath-by-Breath Analysis

Breath-by-breath methods use the same formulas as for mixed expired gas collection. Conceptually, the expired volume is divided into small sequential samples. The volume of each is determined and, when multiplied by the gas concentrations appropriate for that sample (adjusted for the time difference between the flow and gas concentration signals), gives the volume of CO_2 eliminated or O_2 taken up for that sample. The results are summed and then reported either per breath or per unit time. Thus, the phrase "breath-by-breath" applies to the method of expired gas analysis and data reduction and does not necessarily mean that each breath is individually reported.

If V_E is the sum of all volume exhaled between time 0 and time T, then

$$V_E = \sum_{t=0}^{T} V\text{exp}\ (t + \Delta t)$$

where $V\text{exp}(t + \Delta t)$ is the volume expired between time t and $(t + \Delta t)$, Δt is a time interval, and T is the total time of expiration for single or multiple breaths.

This is satisfactory if volume is directly measured over small time intervals. If expired flow rather than volume is measured, then

$$V_E = \int_0^T \dot{V}\text{exp}(t)dt$$

where $\dot{V}\text{exp}(t)$ is the expired flow over the infinitesimally small time interval dt at time t. The volume exhaled over that time is the product $\dot{V}\text{exp}(t) \times dt$. In practice, a small constant Δt is substituted for dt, and the mean flow during the time interval $(t + \Delta t)$ is used as $\dot{V}\text{exp}(t)$:

$$V_E = \sum_{t=0}^{T} \dot{V}\text{exp}\ (t + \Delta t) \times \Delta t$$

where $\dot{V}\text{exp}(t + \Delta t)$ is the mean flow rate during the time interval $t + \Delta t$. The minute ventilation ($\dot{V}_E$) is the volume per unit time.

In a breath-by-breath system, the $\dot{V}CO_2$ is calculated by multiplying the nearly instantaneous F_{ECO_2} for each small time interval by the simultaneous expired volume during that interval. These products are then integrated:

$$VCO_2 = \int_{t=0}^{T} \dot{V}\text{exp}(t)dt \times F_{ECO_2}(t)$$

where $\dot{V}\text{exp}(t)dt$ is the instantaneous expired volume, and $F_{ECO_2}(t)$ is the instantaneous expired CO_2 concentration at time t, adjusted for the delay between when the gas is sampled and when the analyzer reads the appropriate concentration. In practice, the small time interval Δt is substituted for dt:

$$VCO_2 = \sum_{t=0}^{T} \dot{V}\text{exp}(t + \Delta t) \times \Delta t \times F_{ECO_2}(t)$$

where $\dot{V}\text{exp}(t + \Delta t)$ is the mean flow for the time period t to $(t + \Delta t)$, $F_{ECO_2}(t)$ is the mean expired CO_2 during this period, and Δt is a small time interval. For the volume of O_2 taken up, the true O_2 difference $[(\Delta FO_2)\text{true}]$ is substituted for F_{ECO_2} in this equation. The $\dot{V}CO_2$ and $\dot{V}O_2$ are equal to the volume of CO_2 or O_2 divided by the time during exhalation, whether expressed per breath or per minute or other time unit.

An analog-to-digital converter and digital computer perform the necessary multiplications and summations. The respired gas is not, strictly speaking, measured and analyzed continuously, but instead data are rapidly sampled (e.g., every 20 milliseconds). The resultant expired flow versus time curve is, therefore, made up of sequential points sampled at intervals of Δt or at a frequency $f = 1/\Delta t$. The rate of sampling is important because rapid and large changes in expired flow (or gas concentration) may occur during exercise and could be missed if the data are sampled at too slow a rate. Bernard,[13] using generalized simulated curves of expired flow and expired CO_2, found that a sample rate of 30 Hz was adequate during exercise, and that rates of 40, 50, and 100 Hz achieved little improvement in fidelity. Beaver et al.[14] suggested that a sampling frequency equal to twice the highest frequency occurring in the signal to be measured should be used. They suggested that for human exercise testing, a frequency of 50 Hz is satisfactory to record flow and mass spectrometer signals.

A serious potential problem deals with time alignment of the appropriate expired flow (or volume) and expired gas concentration because of the appreciable time required for gas transport and measurement by most gas analyzers. For breath by-breath analysis, it is essential that the appropriate instantaneous flow rate be multiplied by the proper time-matched expired gas concentration. Flow rates can be determined accurately and nearly instantaneously, because flow at the mouth will reach the measuring transducer with a delay determined by the speed of sound (approximately 100 ft/sec) and the distance to the transducer. However, gas analyzer measurements cannot with current technology be made without some delay and distortion inherent to the transport of gas to the analyzer and the intrinsic characteristics of the analyzer. The accuracy of a breath-by-breath system is dependent on the ability of the system to match flow rate and appropriate gas concentration prior to integration. Thus, each flow sampled must be stored until the appropriate expired gas concentration value has been determined. This matching process is performed as part of the computer program for online exercise systems.

Bernard[13] used simulated curves of expired CO_2 and expired flow to estimate potential error caused by the time delay between measurements of these two variables. Using perfectly time-matched hypothetical curves, less than a 5% difference in calculated $\dot{V}CO_2$ was found if the time misalignment was less than or equal to 25 milliseconds. Of importance is that the theoretic sampling rate was 100 Hz, the signals were given random noise, and the product of flow and CO_2 was integrated using the trapezoid rule.

Two factors contribute to the time-alignment problem. Most systems use a capillary tube to draw a continuous expired gas sample into the analyzer. The gas transport time depends on the dimensions of the tube and the flow rate; transport time is on the order of 200 milliseconds. Second, the gas analyzer output itself has an intrinsic response time that further adds to the delay. For infrared CO_2 analyzers, electrochemical O_2 analyzers, and respiratory mass spectrometers, the time constants for response are approximately 50 milliseconds. The result is a delay in the measurement of any instantaneous change in gas concentration at the sampling end of the tubing.

To account for the gas analyzer delay and response time, the transport time plus an additional correction factor are usually used. This function is derived from analysis of the total response of the gas analyzer system. Beaver et al.[14] indicated that the most significant wave shape distortion is removed by a total delay correction equal to transport delay plus one time constant, and analyzed the magnitude of potential errors. We found that an equal-area method for analyzer delay time adds a one-time-constant delay if the analyzer response curve is exponential, and an empirically determined longer delay time if the curve is sigmoid.[15]

The importance of matching flow rate and appropriate gas concentration cannot be overly stressed for a breath-by-breath system. Although not all investigators agree on the optimal way of dealing with gas analyzer response time, a satisfactory balance among degree of accuracy, speed, and reproducibility can be reached.

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Placement of a Brachial Artery Catheter

EQUIPMENT

Appropriate catheter
Cournand-type needle with sharp, hollow stylus
A 2-mL syringe with a 26-gauge needle for local anesthesia
Sterile saline suitable for intravascular injection
Heparinized saline, 50 mL, for catheter flushing

SELECTION OF CATHETER

Because we most often insert the catheter into a brachial artery, we use a polyethylene catheter that is 25 cm long and has a diameter of 1.37 mm. The tip is tapered to fit a guidewire (50.0 cm × 0.63 mm) that fits through a 19-gauge thin-walled Cournand-style needle. The catheter is long enough so that the end used for collection can be brought around the back of the arm and sampling can be done without the subject altering the position of his or her arm or being aware of when blood is sampled.

For radial artery catheterization, any number of small, short polyethylene catheters designed for insertion into the radial artery can be used.

ARTERY SELECTION

The brachial or radial artery is generally used. Complications such as thrombosis are exceedingly rare when appropriate precautions are taken. We find the brachial artery to be preferable, however, because it is larger and the catheter has less effect on compromising its lumen. Moreover, the patient's arm need not be secured to a board, and sliding of the catheter in and out of the artery when the patient moves is not a problem. The radial pulse should be palpated to check for continued patency. If the radial artery is used for the arterial catheterization, perform an Allen test to verify that there is blood flow through the ulnar artery to the hand.

POSITIONING THE ARM FOR BRACHIAL ARTERY CATHETERIZATION

Positioning the arm is extremely important.

1. Extend the arm; place a rolled towel or cushion under the elbow for maximum extension
2. Pronate the hand
3. Palpate the brachial artery on the medial side of the antecubital fossa

LOCAL ANESTHESIA

If the patient is not allergic to the local anesthetic agent, anesthetize the skin and area around the artery. If time allows (approximately 1 hour before placing the catheter), a topical local anesthetic ointment (e.g., lidocaine plus prilocaine) can be used to anesthetize the skin surface. For injection, we use 1% or 2% lidocaine without epinephrine. After positioning the arm, inject the local anesthetic (1) intradermally above the artery, (2) subcutaneously just above the artery, and (3) subcutaneously on either side of the artery. The total amount should be about 1 to 2 mL, because excessive amounts of anesthetic can make palpation of the brachial pulse more difficult.

ARTERIAL PUNCTURE AND CATHETER INSERTION

1. Locate the artery between the fingers in the area of anesthesia.
2. Use a 19-gauge Cournand-style needle with the sharp, hollow stylus inserted.
3. Holding the needle by its shield while keeping the stylus in the needle with one's thumb (be sure not to cover the hole in the stylus), penetrate the skin over the artery. Position the tip of the needle above the artery. Then abruptly insert the stylus and the needle tip into the artery.
4. When the tip of the stylus enters the artery, blood will flow out of the proximal hole in the stylus.
5. Advance the needle 1 mm to be sure that the tip of the needle is in the artery (the stylus protrudes a little beyond the tip of the needle).
6. Remove the stylus. At this point, blood should shoot out of the needle with arterial pressure, indicating that the needle tip is well within the lumen of the artery. If blood does not flow readily, withdraw the needle slightly (it might have gone into the posterior wall of the artery). Once a strong stream of arterial blood is evident, it is safe to advance the needle further into the lumen of the artery using the

continuous stream of blood to document the needle's position. The needle advance may be facilitated by depressing the hub slightly to reduce the possibility of impaling the posterior wall of the artery with the needle tip. Do not advance the needle without the stylus in place if there is no flow of blood. It may damage the artery.

7. If there is no blood flow, slowly withdraw the needle without the stylus because the needle tip may have passed through the inner wall of the artery. If there is still no blood flow, withdraw the tip of the needle to the skin. Clear the needle and stylus of any blood or clot, and then try again.
8. With the needle tip in the lumen of the artery (documented by freely flowing blood), thread the guidewire for the catheter through the needle and slide it about 3 inches into the lumen of the artery. If the guidewire does not slip easily past the needle tip, the needle lumen is not centered in the lumen of the artery, and the needle must be repositioned. Do not try to advance the guidewire if any resistance is encountered.
9. Remove the needle, leaving the guidewire in place. To avoid a hematoma at the site, compress over the site at which the needle was inserted because the guidewire is narrow relative to the withdrawn needle.
10. Now slide the smoothly tapered end of the catheter over the wire. When the catheter reaches the skin, slide it through the skin and arterial wall using a gently rotating motion while holding the skin back so that it does not move with the catheter.
11. When the catheter is well established several inches into the artery, remove the guidewire. Blood should readily flow out of the end of the catheter.
12. Attach a Luer-lock stopcock to the end of the catheter and flush the system immediately with heparinized saline.
13. Cover the site of insertion with sterile gauze and fix the catheter with tape.

DIFFICULT PUNCTURES

Limit yourself to 15 minutes of effort. If you are not successful by then, stop trying and ask someone with more experience to help or rely only on noninvasive measurements. The latter will provide a considerable amount of information.

Appendix E

Tables and Nomogram

Table E.1

Partial Pressure of Water of Saturated Gas at Centigrade Temperature *T*

T	P_{H_2O}	T	P_{H_2O}	T	P_{H_2O}	T	P_{H_2O}	T	P_{H_2O}
10	9.20	17	14.53	24	22.38	31	33.70	38	49.70
11	9.84	18	15.47	25	23.76	32	35.67	39	52.45
12	10.51	19	16.47	26	25.21	33	37.73	40	55.34
13	11.23	20	17.53	27	26.74	34	39.90		
14	11.98	21	18.65	28	28.35	35	42.18		
15	12.78	22	19.82	29	30.04	36	44.57		
16	13.63	23	21.07	30	31.83	37	47.08		

Table E.2

Factors for Conversion from ATPS to BTPS (37°C)

T°C	P_B	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
	600	1.138	1.132	1.126	1.120	1.115	1.109	1.103	1.097	1.090	1.084	1.078	1.071	1.065	1.058	1.051
	610	1.136	1.131	1.125	1.119	1.114	1.108	1.102	1.096	1.090	1.083	1.077	1.071	1.064	1.058	1.051
	620	1.135	1.130	1.124	1.118	1.113	1.107	1.101	1.095	1.089	1.083	1.076	1.070	1.064	1.057	1.050
	630	1.134	1.129	1.123	1.117	1.112	1.106	1.100	1.094	1.088	1.082	1.076	1.069	1.063	1.056	1.050
	640	1.133	1.128	1.122	1.116	1.111	1.105	1.099	1.093	1.087	1.081	1.075	1.069	1.062	1.056	1.049
	650	1.132	1.127	1.121	1.116	1.110	1.104	1.098	1.092	1.087	1.081	1.074	1.068	1.062	1.056	1.049
	660	1.131	1.126	1.120	1.115	1.109	1.103	1.098	1.092	1.086	1.080	1.074	1.068	1.061	1.055	1.049
	670	1.130	1.125	1.119	1.114	1.108	1.103	1.097	1.091	1.085	1.079	1.073	1.067	1.061	1.055	1.048
	680	1.129	1.124	1.118	1.113	1.107	1.102	1.096	1.090	1.085	1.079	1.073	1.067	1.060	1.054	1.048
	690	1.128	1.123	1.118	1.112	1.107	1.101	1.095	1.090	1.084	1.078	1.072	1.066	1.060	1.054	1.047
	700	1.128	1.122	1.117	1.111	1.106	1.100	1.095	1.089	1.083	1.077	1.072	1.066	1.059	1.053	1.047
	710	1.127	1.121	1.116	1.111	1.105	1.100	1.094	1.088	1.083	1.077	1.071	1.065	1.059	1.053	1.047
	720	1.126	1.121	1.115	1.110	1.104	1.099	1.093	1.088	1.082	1.076	1.070	1.065	1.059	1.052	1.046
	730	1.125	1.120	1.115	1.109	1.104	1.098	1.093	1.087	1.082	1.076	1.070	1.064	1.058	1.052	1.046
	740	1.124	1.119	1.114	1.109	1.103	1.098	1.092	1.087	1.081	1.075	1.070	1.064	1.058	1.052	1.046
	750	1.124	1.118	1.113	1.108	1.102	1.097	1.092	1.086	1.080	1.075	1.069	1.063	1.057	1.051	1.045
	760	1.123	1.118	1.113	1.107	1.102	1.096	1.091	1.086	1.080	1.074	1.069	1.063	1.057	1.051	1.045
	770	1.122	1.117	1.112	1.107	1.101	1.096	1.090	1.085	1.079	1.074	1.068	1.062	1.057	1.051	1.045
	780	1.122	1.116	1.111	1.106	1.101	1.095	1.090	1.084	1.079	1.073	1.068	1.062	1.056	1.050	1.044

T°C, ambient temperature in degrees centigrade; P_B, barometric pressure.

Table E.3

Factors for Conversion from ATPS to STPD

T°C	PB	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
	600	0.729	0.725	0.722	0.718	0.714	0.710	0.706	0.703	0.699	0.695	0.691	0.686	0.682	0.678	0.674
	610	0.741	0.738	0.734	0.730	0.726	0.723	0.719	0.715	0.711	0.707	0.703	0.698	0.694	0.690	0.685
	620	0.754	0.750	0.746	0.742	0.739	0.735	0.731	0.727	0.723	0.719	0.715	0.710	0.706	0.702	0.697
	630	0.766	0.762	0.759	0.755	0.751	0.747	0.743	0.739	0.735	0.731	0.727	0.722	0.718	0.714	0.709
	640	0.779	0.775	0.771	0.767	0.763	0.759	0.755	0.751	0.747	0.743	0.739	0.734	0.730	0.726	0.721
	650	0.791	0.787	0.783	0.779	0.775	0.771	0.767	0.763	0.759	0.755	0.751	0.746	0.742	0.737	0.733
	660	0.803	0.800	0.796	0.792	0.788	0.784	0.780	0.775	0.771	0.767	0.763	0.758	0.754	0.749	0.745
	670	0.816	0.812	0.808	0.804	0.800	0.796	0.792	0.788	0.783	0.779	0.775	0.770	0.766	0.761	0.757
	680	0.828	0.824	0.820	0.816	0.812	0.808	0.804	0.800	0.795	0.791	0.787	0.782	0.778	0.773	0.768
	690	0.841	0.837	0.833	0.829	0.824	0.820	0.816	0.812	0.807	0.803	0.799	0.794	0.790	0.785	0.780
	700	0.853	0.849	0.845	0.841	0.837	0.832	0.828	0.824	0.820	0.815	0.811	0.806	0.802	0.797	0.792
	710	0.866	0.861	0.857	0.853	0.849	0.845	0.840	0.836	0.832	0.827	0.823	0.818	0.813	0.809	0.804
	720	0.878	0.874	0.870	0.865	0.861	0.857	0.853	0.848	0.844	0.839	0.835	0.830	0.825	0.821	0.816
	730	0.890	0.886	0.882	0.878	0.873	0.869	0.865	0.860	0.856	0.851	0.847	0.842	0.837	0.833	0.828
	740	0.903	0.899	0.894	0.890	0.886	0.881	0.877	0.872	0.868	0.863	0.859	0.854	0.849	0.844	0.840
	750	0.915	0.911	0.907	0.902	0.898	0.894	0.889	0.885	0.880	0.875	0.871	0.866	0.861	0.856	0.851
	760	0.928	0.923	0.919	0.915	0.910	0.906	0.901	0.897	0.892	0.887	0.883	0.878	0.873	0.868	0.863
	770	0.940	0.936	0.931	0.927	0.923	0.918	0.913	0.909	0.904	0.900	0.895	0.890	0.885	0.880	0.875
	780	0.953	0.948	0.944	0.939	0.935	0.930	0.926	0.921	0.916	0.912	0.907	0.902	0.897	0.892	0.887

T°C, ambient temperature in degrees centigrade; PB, barometric pressure.

Table E.4

Estimated Oxygen Uptake ($\dot{V}o_2$) for Various Activities

Activity	Estimated $\dot{V}o_2$ (mL/kg/min)
Basic postures	
Sitting only (desk work, writing, calculating)	4.25
Standing only (bartending)	8.75
Walking 3.0 mph	10.5
Walking 3.5 mph	14.0
Sitting: Light or moderate work	
Driving a car	4.25
Driving a truck	5.30
Hand tools, light assembly	5.30
Working heavy levers	7.0
Riding a mower	8.75
Crane operator	8.75
Driving heavy truck (including frequent on and off with some arm work)	10.5
Standing: Moderate work	
Light assembly at slow pace	8.75
Gas station operator	9.45
Scrubbing, waxing, polishing (floors, walls)	9.45
Heavy assembly (farm machinery, plumbing)	10.5
Light welding	10.5
Stocking shelves (light objects)	10.5
Janitorial work	10.5
Assembly line with light or medium parts at moderate pace	12.25
Assembly line with brief lifting every 5 minutes (45 lb or less)	12.25
Same as above (parts > 45 lb)	14.0
Hitching trailers, operating jacks or heavy levers	12.25
Masonry, painting, paperhanging	14.0
Walking: Moderate work	
Carrying trays, dishes	14.70
Gas station mechanical work (changing tires, etc.)	15.75
Heavy arm work	
Lifting and carrying	
20–44 lb	15.75
45–64 lb	21.0
65–84 lb	26.25
85–100 lb	29.75
Heavy tools	
Jackhammers, pneumatic drills	21.0
Shovel, pick	28.0
Carpentry	
Light interior repair (tile laying)	14.0
Building and finishing interior	15.75
Putting in sidewalk	17.5
Exterior remodeling (hammering, sawing)	21.0
Miscellaneous	
Pushing objects of 75 lb or more (desks, file cabinets)	28.0
Laying railroad track	24.5
Cutting trees or chopping wood	
Hand saw	19.25
Automatic	10.5

From Tennessee Heart Association. *Physician's Handbook for Evaluation of Cardiovascular and Physical Fitness*. Nashville, TN: Tennessee Heart Association; 1972, with permission.

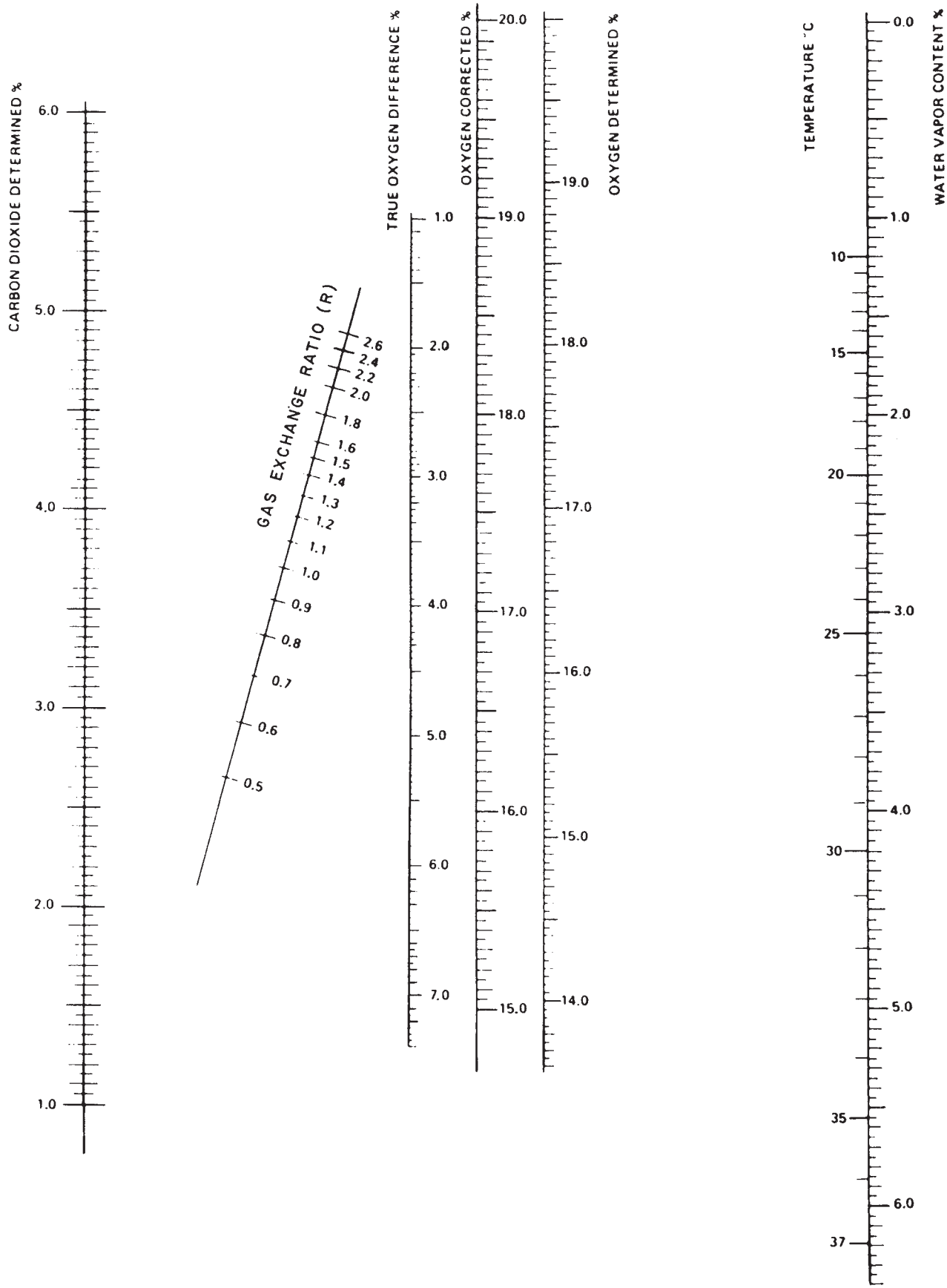

FIGURE E.1. Nomogram for computing true O_2 difference [(ΔFO_2)true] and gas exchange ratio (R) from a sample of expired gas, using values of expired CO_2 ($FECO_2$) and expired O_2 (FEO_2) present in a wet sample whose water vapor content is known or, if the sample is saturated with water, whose temperature is known. (Modified from Beaver WL. Water vapor corrections in oxygen consumption calculations. *J Appl Physiol.* 1973;35:928–931.)

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