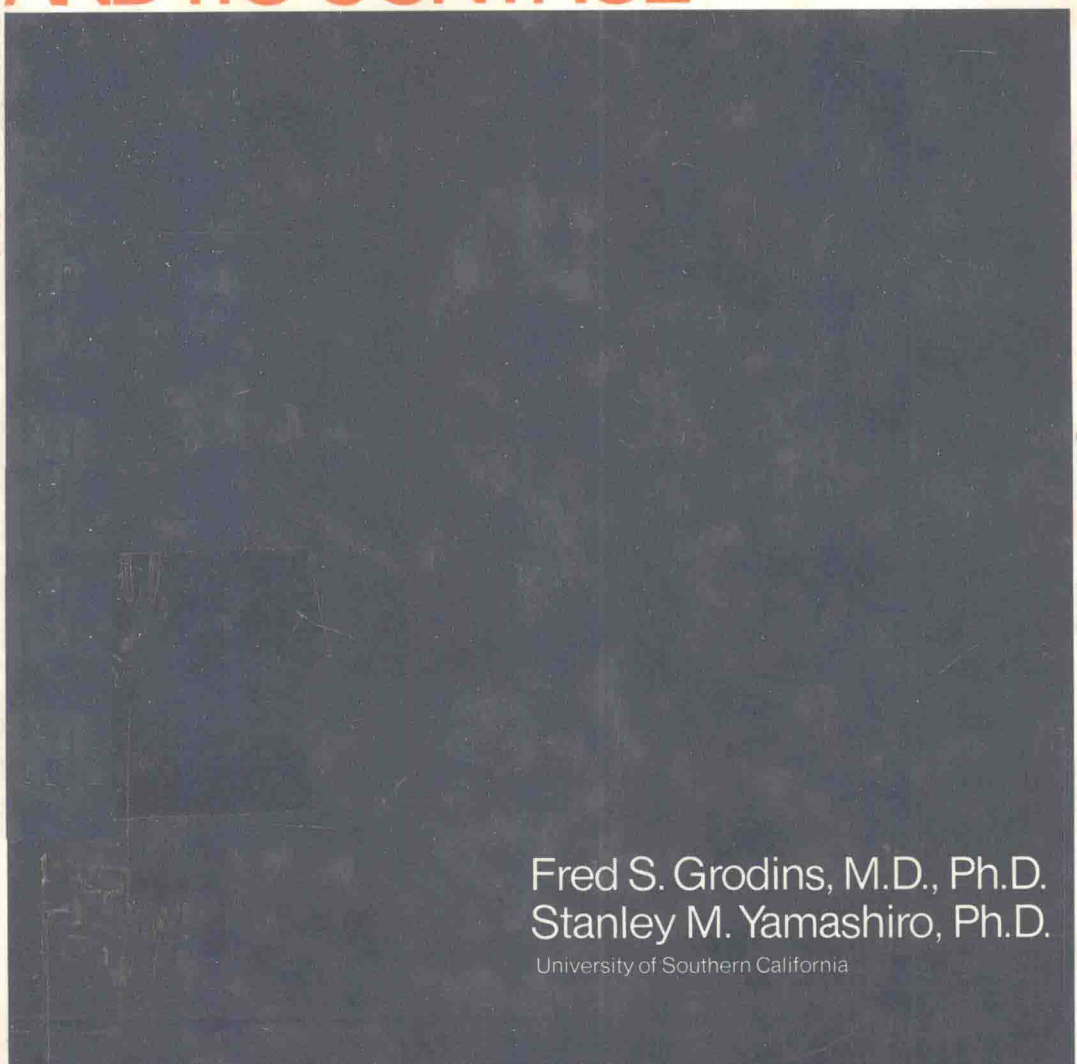
MODERN CONCEPTS
IN MEDICAL PHYSIOLOGY

RESPIRATORY FUNCTION OF THE LUNG AND ITS CONTROL



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Respiratory Function of the Lung and Its Control

MODERN CONCEPTS IN MEDICAL PHYSIOLOGY

A MACMILLAN SERIES

Lysle H. Peterson, M.D., Consulting Editor

Preface

THIS BOOK HAS EVOLVED from hand-out lecture notes used for many years in teaching respiratory physiology to medical students and to graduate and senior undergraduate students in physiology, biology, and biomedical engineering. It should also be of interest to specialists in anesthesiology, pulmonary medicine, and respiratory therapy. The text is organized to stress the analysis-synthesis dual approach essential in modern systems physiology. An introductory survey describes the components of the system and their organization into a metabolic servomechanism that meets metabolic demands for oxygen and CO_2 transport while regulating against hypoxia and disturbances in acid-base balance. After a brief review of the gas laws and their applications in respiration (Chapter 2), the next four chapters analyze the components in detail: "The Ventilatory Apparatus" (Chapter 3), "The Pulmonary Gas Exchanger" (Chapter 4), "Tissue Gas Exchange" (Chapter 5), and "Blood Buffers and Acid-Base Balance" (Chapter 6). Chapter 7 ("Control of Pulmonary Ventilation") is a synthesis, using the theme of control and communication (homeostasis, cybernetics) to emphasize the interactions between the several components as they respond to physiologic and pathologic demands in health and disease.

Many sources, both written and unwritten, have contributed to this effort over some 30 years. It is impossible to acknowledge all of them, but one whose influence is clearly evident throughout is John S. Gray, the former teacher and colleague of one of us (FSG) at Northwestern University Medical School from 1947–1967. We dedicate this book to him.

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Respiratory Function of the Lung and Its Control

Contents

CHAPTER

1

Introductory Survey of the Respiratory System

THE OVERALL BEHAVIOR of the respiratory system in man is an expression of the integrated interaction of many different unit processes. To understand this behavior, we must examine both the unit processes and their interactions. That the latter are at least as important as the former is clear from the fact that a single set of unit processes may be "programmed" to perform a great variety of overall tasks (e.g., in the analog or digital computer). An approach that emphasizes an understanding of the overall behavior of complex systems in terms of interacting unit processes has been formally recognized in recent years under the name *Systems Analysis*. In a sense, this is a misnomer, for the really new feature is the emphasis on synthesis. Analysis, after all, has been with us since the dawn of science. An important type of interaction that occurs frequently in biologic systems is negative feedback, and it is rewarding to examine such systems in the framework of control theory. This is the approach we shall adopt in our study of respiration.

How small should our unit processes be? There is no unique answer to this question except to say that they should be small enough to contribute to useful understanding but not so small as to introduce unnecessary complication and confusion at the overall level of primary interest. This may not seem to be a very satisfactory answer, but fortunately we are reasonably successful at making proper intuitive choices in practice. Thus none of us would try to understand the overall behavior of an automobile in terms of the elementary nuclear

particles of which it is composed, even though we acknowledge their ultimate relevance. To the busy clinician pressed for time and committed to prompt action, explicit analysis of disease in terms of any unit process smaller than the "whole man" may seem an unnecessary luxury. Nevertheless, we are certain that he does make such an analysis implicitly and that it contributes significantly to sound clinical judgment.

What are the overall functions of the respiratory system? The most obvious one is oxygen procurement and carbon dioxide elimination at rates required by tissue metabolism. Since no significant oxygen stores exist in the body, a continuous external supply is essential for survival. Thus man can live weeks without food, days without water, but only a few minutes without oxygen. In exercise, tissue oxygen requirements may increase tenfold, and this demand must be promptly met. To do so requires a cooperative effort by the respiratory (external procurement) and cardiovascular (internal transport and distribution) systems, which are inseparably coupled in this task of metabolic gas transport and exchange. Not only must gross oxygen exchange rate be adequate but efficient tissue utilization requires that it be accomplished at sufficiently high levels of internal oxygen concentration. The nervous system is particularly sensitive to low oxygen concentration, and, in most common types of hypoxia, it is the internal concentration rather than the gross exchange rate that is low. Considerations of this sort lead us to look at the O_2 procurement and CO_2 elimination functions of respiration from another point of view, one that lies at the heart of physiology, i.e., homeostasis, or regulation.

Thus, instead of saying that the function of respiration is to procure O_2 and eliminate CO_2 at rates required by tissue metabolism, we can say that its function is to regulate arterial blood concentrations of O_2, CO_2, and H^+ within prescribed limits. This view is a much more powerful and general one and implies the existence of active control processes that would not otherwise be necessary. For example, a single cell in direct contact with its external environment through a passive membrane could procure O_2 and eliminate CO_2 by simple diffusion at rates required by its metabolism, provided its internal O_2 concentration were allowed to fall and its internal CO_2 concentration to rise sufficiently to establish the necessary concentration gradients. But this is a very restricted process, for internal P_{O_2} obviously cannot fall below zero and internal P_{CO_2} cannot rise too high without producing fatal increases in acidity. If, on the other hand, we had an active membrane that could "pump" O_2 into and CO_2 out of the cell, and if its pumping rates depended in appropriate ways upon internal O_2 and CO_2 concentrations, we could "automatically" match exchange rates to metabolism over a much wider range with minimal changes in internal

concentrations. Not only could we do that, but we could also automatically guard against other kinds of disturbances that might threaten internal concentrations, e.g., increased CO_2 in the external environment, or increased production of "fixed acids" by a faulty metabolic machinery.

It turns out that we can bring these two views together in the context of control and servomechanism theory. Thus we can say that what we have here is a metabolic servomechanism designed to match pulmonary and metabolic gas exchange rates without alteration of internal chemical concentrations by active manipulation of pulmonary ventilation, and whose error-correcting feedback signals are provided by the concentrations of O_2, CO_2, and H^+ in arterial blood. As we shall see in later chapters, it is much easier to identify the error-correcting chemical feedback signals than it is to find the "metabolic command signal" that should provide the servosystem's primary input.

What basic structures and unit processes do we encounter in exploring the details of our respiratory metabolic servomechanism? It is not difficult to list them proceeding from the "outside in":

1. There is a mechanism for the bulk transfer of gas between the external atmosphere and the internal gas phase in the lung alveoli. This utilizes a "bellows" technique, i.e., the alternate expansion and compression of a hollow chamber in communication with the atmosphere. The energy to operate the bellows comes from the respiratory muscles. We shall collectively call all of the structures concerned the *ventilatory apparatus* and the unit process *pulmonary ventilation.*

2. There is a mechanism for the transfer of gases between the internal gas phase and the blood in the pulmonary capillaries. The mechanism is one of passive diffusion which follows well-known physicochemical laws. We shall call the structures concerned the *pulmonary diffusion apparatus* and the unit process *pulmonary diffusion.*

3. There is an internal transport medium (the blood) so structured that it can carry sufficient O_2 and CO_2 to meet tissue needs within existing constraints imposed by ambient P_{O_2}, pulmonary ventilation rates, blood flow rates, and permissible internal concentrations of H^+. We shall call this medium the *blood chemical apparatus* and the unit process *blood chemical processing.*

4. There is an internal pumping and distribution system to move blood from lungs to tissues and back again. We shall call this structural component the *cardiovascular system* and the unit process *circulation.*

5. There is a mechanism for transferring O_2 and CO_2 between blood in the systemic capillaries and the tissues. Again, it is accomplished by passive diffusion. We call this the *tissue diffusion apparatus* and the unit process *tissue diffusion.*

6. Finally, we have the metabolizing tissues themselves which consume oxygen at a rate, $\dot{V}_{O_2}$ L/min, and produce CO_2 at a rate, $\dot{V}_{CO_2}$ L/min. The ratio of these two tissue rates, $\dot{V}_{CO_2}/\dot{V}_{O_2}$, is called the "respiratory quotient," RQ. We shall call this component the *metabolic system* and the unit process *tissue metabolism.*

We can summarize the system so far described by tracing the flow of O_2 and CO_2 through the "hardware diagram" in Figure 1-1. Numerical values for important respiratory quantities are given in the diagram for a resting man breathing atmospheric air at sea level. The ventilatory apparatus on the left is connected to the metabolizing tissues on the right by the cardiovascular system that lies between.

Atmospheric air with an oxygen partial pressure ($P_{I_{O_2}}$) of 160 mm Hg and a CO_2 partial pressure ($P_{I_{CO_2}}$) of essentially zero enters the lung alveoli during inspiration. Here it is exposed to mixed venous blood entering the pulmonary capillaries with a $P_{V_{O_2}}$ of 43 mm Hg and a $P_{V_{CO_2}}$ of 47 mm Hg. Passive diffusion of O_2 from air to blood and of CO_2 from blood to air thus takes place across the alveolocapillary membrane until equilibrium is reached at a P_{O_2} of 103 mm Hg and a P_{CO_2} of 40 mm Hg. The equilibrated air, which now contains less O_2 and more CO_2 than inspired air, is called "alveolar air" ($P_{A_{O_2}} = 103$; $P_{A_{CO_2}} = 40$), and the equilibrated blood, which now contains more O_2 and less CO_2 than mixed venous blood, is called "end capillary blood" ($P_{ec_{O_2}} = 103$; $P_{ec_{CO_2}} = 40$). The alveolar air now leaves the lung during expiration, mixes with air of inspired composition that remained in the "dead space" (i.e., the conducting, nonexchanging airways) at the end of the previous inspiration, and becomes expired air with a composition intermediate between that of inspired and alveolar air ($P_{E_{O_2}} = 115$; $P_{E_{CO_2}} = 29.5$). End capillary blood leaving the lung normally mixes with a small amount of blood of venous composition that bypasses the lungs through anatomical shunt pathways (chiefly the bronchial circulation), and the mixture is called arterial blood. The properties of the blood chemical processor are such that this small "venous admixture" produces no detectable change in $P_{ec_{CO_2}}$, so that $P_{a_{CO_2}} = P_{ec_{CO_2}} = P_{A_{CO_2}}$; however, it does produce an appreciable drop (8 mm Hg) in $P_{ec_{O_2}}$, so that $P_{a_{O_2}} < P_{ec_{O_2}} = P_{A_{O_2}}$. The left heart pumps the arterial blood to the tissues, which actively consume oxygen ($\dot{V}_{O_2} = 0.275$ L/min) and produce CO_2 ($\dot{V}_{CO_2} = 0.234$ L/min) and in so doing set up diffusion gradients across the tissue-capillary gas exchanger. Passive diffusion of O_2 from blood to tissue and of CO_2 from tissue to blood therefore occurs across the capillary membrane, and the blood leaves the tissue exchanger as mixed venous blood with $P_{V_{O_2}} = 43$ and $P_{V_{CO_2}} = 47$. This blood is pumped back to the pulmonary exchanger and the exchange cycle begins again. In the steady state, the gas exchange rates across the lung, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and their ratio, R (the

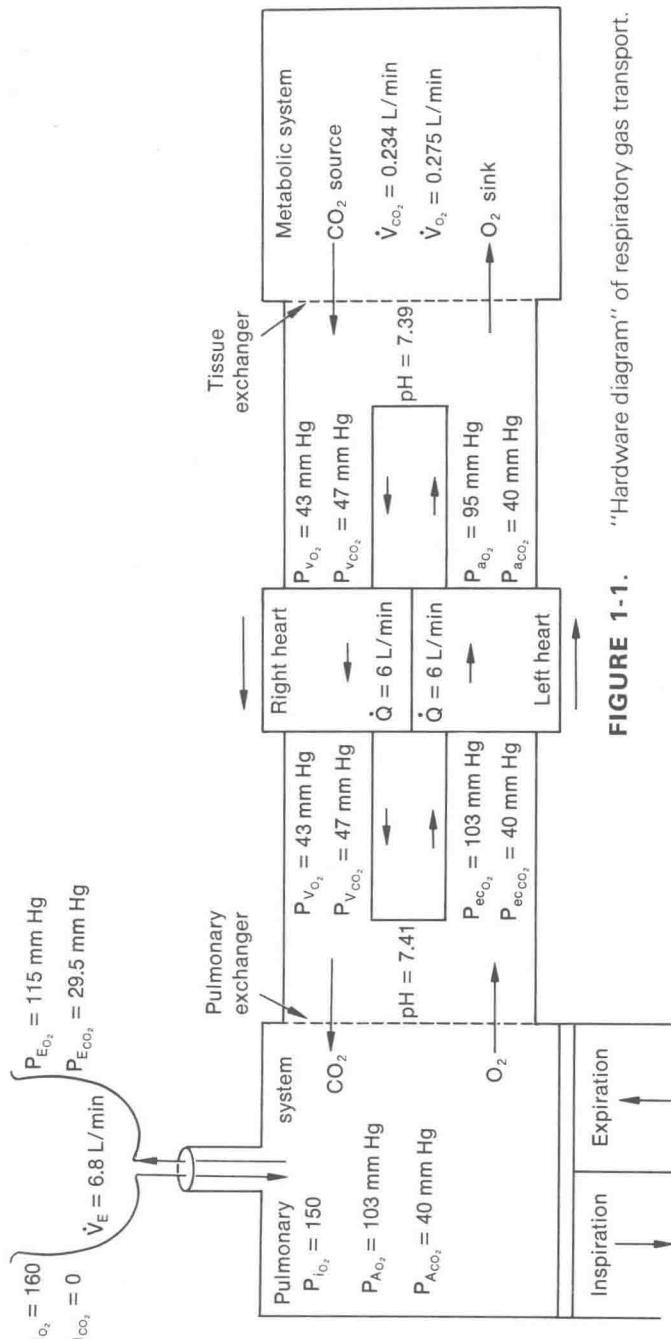

FIGURE 1-1. "Hardware diagram" of respiratory gas transport.

"respiratory exchange ratio"), measured by analysis of inspired and expired air, are equal to the corresponding tissue metabolic rates of O_2 consumption and CO_2 production and their ratio, RQ (the respiratory quotient), in the metabolic system. However, since there is a large storage capacity for CO_2 in the body, transient states may occur during which $\dot{V}_{CO_2}$, and thus R, measured across the lung, are not equal to the metabolic CO_2 production rate and RQ. The value of the metabolic respiratory quotient, RQ, depends only upon the food material being oxidized, ranging from 0.7 for a pure fat substrate to 1.0 for pure carbohydrate, and averaging about 0.85 on a normal mixed diet. However, the expired respiratory exchange ratio, R, will fall below RQ if body CO_2 stores are increasing or rise above it if these stores are decreasing during transient states.

Although both air pumping by the ventilatory apparatus and blood pumping by the heart are cyclic rather than continuous processes, it is customary to average the volumes pumped over a 1-min period and to call this average *pulmonary ventilation* for the lung pump ($\dot{V}_E$ = 6.8 L/min) and "cardiac output" for the heart pump ($\dot{Q}$ = 6.0 L/min). In severe exercise when $\dot{V}_{O_2}$ may rise over tenfold to 3.5 L/min, $\dot{V}_E$ increases to 120 L/min, and $\dot{Q}$ to 35 L/min.

Figure 1-1 is a material flow diagram in which we can conveniently trace the flow of O_2 and CO_2 through the lung-blood-tissue respiratory complex. However, it has nothing to say about the operation of our metabolic servosystem. To examine this, we need a different sort of block diagram and this appears in Figure 1-2.

This diagram conforms in pattern and purpose to a feedback control system. In constructing it, we have assumed that the respira-

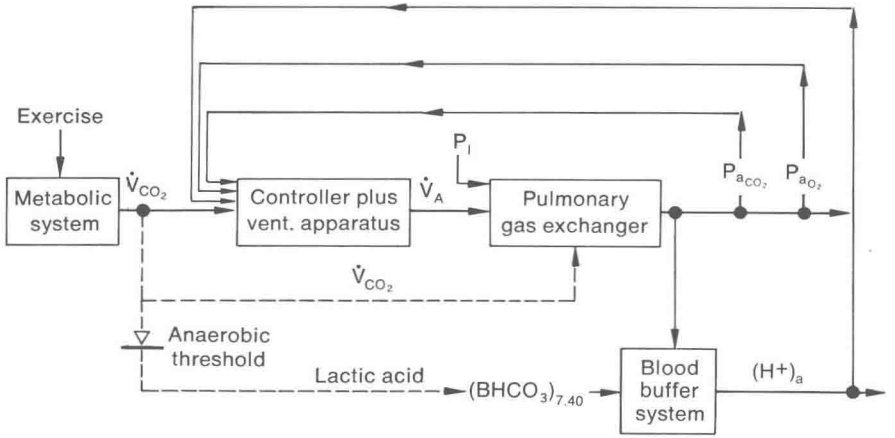

FIGURE 1-2. Diagram of the "Metabolic Servomechanism."

tory system comprises a metabolic servomechanism designed to match pulmonary and metabolic gas exchange rates over a wide range with no change in arterial composition. We have further assumed that it does this by providing the "controller" block with a "command signal" telling it to vary $\dot{V}_E$ in direct proportion to $\dot{V}_{CO_2}$. If the controller does this, then the outputs of the "process," $P_{a_{CO_2}}$, $P_{a_{O_2}}$, and $(H^+)_a$, will remain constant. If it does not, then these outputs will change. Hence, if their values are sensed and "fed back" to the controller, the latter will be informed of its degree of success in matching external gas exchange to metabolic needs and can correct any "error." Because of the nature of its feedback, this system will also act as a regulator to partially correct any deviations in $P_{a_{CO_2}}$, $P_{a_{O_2}}$, and $(H^+)_a$ brought about by such disturbances as CO_2 inhalation, altitude hypoxia, and metabolic acidosis.

In the chapters to follow, we shall seek to understand the operation of this metabolic servosystem through the complementary processes of analysis and synthesis. We shall begin with a brief review of the gas laws, which are essential tools in the study of respiratory physiology.

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CHAPTER

2

Gas Laws and Applications

Ideal Gas

EXPERIMENTALLY, IT HAS BEEN FOUND that all gases behave essentially in the same way provided temperatures are not too low and pressures are not too high. Thus the volume, V, occupied by a mass, m, of any kind of gas depends on the pressure, P, to which the gas is subjected, and on its temperature, T. This interrelationship is neatly summarized by the empirical equation of state of an ideal gas:

$$PV = nRT \tag{1}$$

The quantity, n, refers to the mass in terms of the number of moles ($n = m/M$, M = molecular weight) and R is the universal gas constant. In physiology, volumes are commonly expressed in liters, pressures in millimeters of mercury or centimeters of water, and temperatures in degrees centigrade (or degrees Kelvin). In this system of units,

$$R = 62.37 \frac{\text{liter} \cdot \text{mm Hg}}{\text{mole} \cdot {}^\circ\text{K}}$$

if pressure is measured in millimeters of mercury.

All real gases deviate from ideal gas behavior, especially at high pressures. However, over the physiologic range of pressures, most gases can be adequately described by equation (1). For a fixed mass (or

fixed number of moles) and a constant temperature, equation (1) becomes

$$PV = \text{const} \tag{2}$$

The observation that the product of pressure and volume of a fixed mass of gas at constant temperature is constant was first made by Robert Boyle in 1660. As we shall see later, this equation has many applications in respiratory mechanics.

Dalton's Law

In a mixture of gases, such as occurs in the atmosphere or the lung, the total pressure is equal to the sum of the pressures exerted by its component gases. These separate pressures are called the partial pressures of the components. The partial pressure of each gas in the mixture is the same pressure that would be present if the gas occupied the entire mixture volume alone. Thus each gas in a mixture behaves independently of the others. This fact is known as Dalton's law. The partial pressure, P_g, of a gas is often described as

$$P_g = F_g B \tag{3}$$

where F_g is the volumetric fraction of the gas and B is the total pressure of the mixture.

Water Vapor

One gas that requires special treatment is water vapor. Unlike the other respiratory gases, water is a liquid at ordinary temperatures. The maximum partial pressure of water in a wet gas at a given temperature is equal to the vapor pressure of water at that temperature. Table 2-1 shows how the vapor pressure of water varies as a function of temperature. When the partial pressure of water in a wet gas is equal to its maximum value at the existing temperature, the gas is said to be saturated with water vapor. Relative humidity of a gas is defined as the ratio of the actual partial pressure of water to the vapor pressure at the same temperature, i.e.,

$$\text{relative humidity (\%)} = \frac{100 \times \text{partial pressure of water vapor}}{\text{vapor pressure at same temperature}}$$

If the vapor is in contact with an excess of liquid, then saturation (100% relative humidity) is insured. Thus, in the lung or wet