# Respiratory Physiology

SECOND EDITION

Allan H. Mines

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# Respiratory Physiology
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*Raven Press Series in Physiology*

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# *Preface*

During my 23 years of teaching medical physiology to about 7,000 students, I have experimented with many different instructional approaches to each subject. Some of these proved ineffective and were dropped. The techniques that I found most effective have been retained and refined, and are used in this text. The author, and any students who may find this book useful, are indebted to these student "guinea pigs" of mine.

What sort of book is it? It is especially tailored to help students taking a course in medical physiology gain a working knowledge of respiratory physiology. The material I have selected for inclusion and the order in which I have presented it represent my best attempt to expedite this process. Reasonable teachers can (and undoubtedly will) disagree with my choices. I apologize to them in advance.

I have also chosen to include problems and problem answers at the end of each chapter. These are an important part of the text. I agree with most educators that memorization of normal values and equations, and learning to understand concepts, are necessary steps in a medical student's education. I do not believe students have acquired the most relevant education, however, until they can solve nontrivial problems by using their knowledge. Thus, solving the problems at the end of each chapter requires the application of previously acquired information to new situations, some of them clinical. The answers to the problems identify not only the correct numerical result, or the correct alternative choice, but also present some of the logical sequences that might have been used in arriving at those answers.

This volume will be of interest as a course textbook to medical students, allied health students, and graduate academic students in physiology and related subjects. Advanced students, physicians, and researchers interested in reviewing the basic physiology of the human respiratory system may also find this text useful.

ALLAN H. MINES

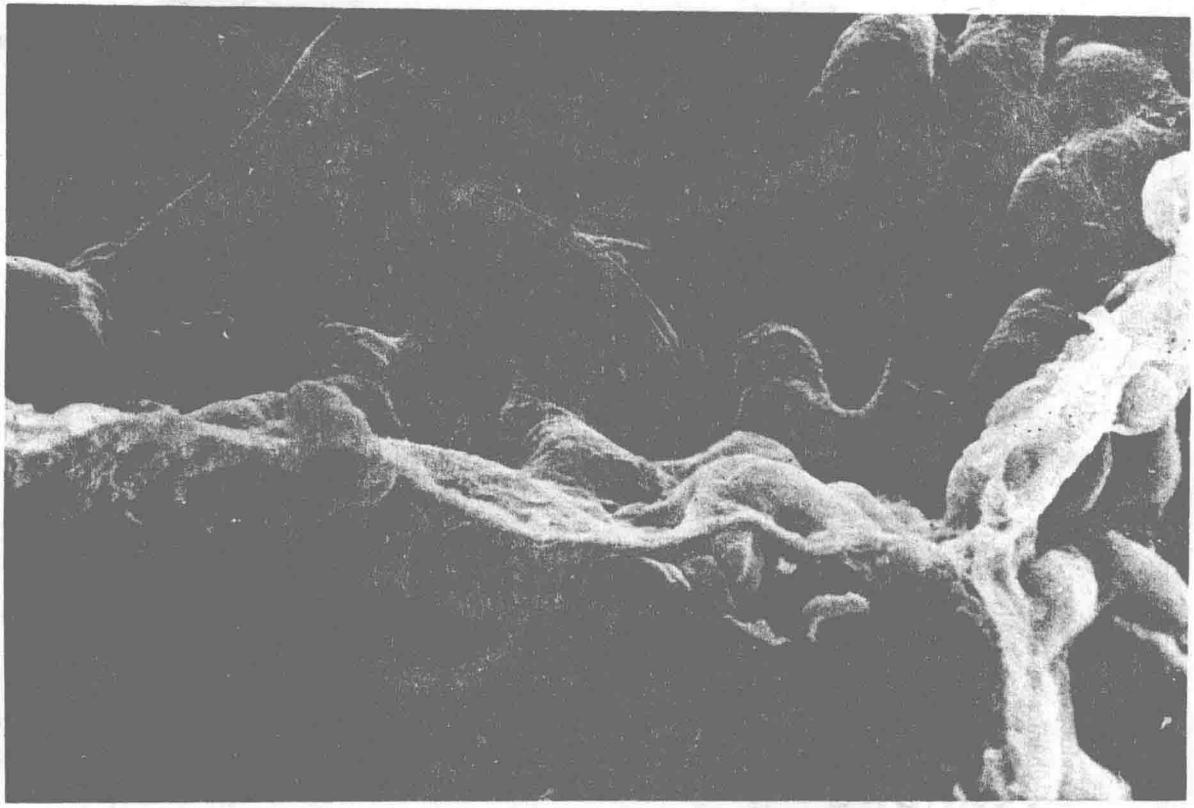
# *Acknowledgments*

I would like to thank Ms. Jeanne Ashe for preparing the manuscript. Her flying fingers and consistent attention to detail are remarkable.

My thanks go to Anne Rothman for preparing the drawings.

I am grateful to my wife, Susan, for proofreading the various stages of this text. She endured my wordiness and misspellings with equal patience.

Finally, I owe a debt to my students, on whom I have tried many of the approaches which appear in this text, as well as many others (which mercifully do not appear). I hope to repay that debt in some small way by making the study of respiratory physiology somewhat easier for students to come.



A scanning electron micrograph showing parts of three alveoli in mammalian lung. Note the richness of the blood supply. The blood vessels are packed together such that there is almost a "sheet" of blood within the alveolar septa. Note also that there is an ultra thin (≃ 1 $\mu$m) barrier between erythrocytes and alveolar gas. Micrograph courtesy of Ewald Weibel, M.D.

# *Contents*

# 1

# *Introduction to Respiration*

Respiration is often divided into two parts: internal respiration and external respiration. The former deals with the processes by which the mitochondria metabolize various foodstuffs, usually involving $O_2$ as the oxidizing agent, and resulting in the production of high energy bonds, $CO_2$ and $H_2O$. This subject is adequately covered in any good textbook of biochemistry, and will hardly be mentioned here. The latter, external respiration, which involves the exchange of gases between the environment and the mitochondria, is the subject of this book. The first chapter is designed to give an overview of respiration: It begins with a consideration of the structure of the system from several viewpoints, and then goes into a brief description of the muscles of respiration. The symbols for variables that are commonly used in respiratory physiology are then tabulated and defined in Table 1. Next, two simple models of the respiratory system are discussed, followed by a section dealing with ideal gas volume conversions and a brief consideration of the control systems that regulate our breathing. The chapter ends with the definition of the various lung volumes, and with some examples of their measurement using common methods.

## STRUCTURE

A brief consideration of the anatomy of the system is probably warranted, since an understanding of function so often depends on a knowledge of the underlying structure. The human lung is extremely complex. The main conducting tube, the trachea, divides into two bronchi, which in turn divide into two tubes each, and each of these tubes then divides into two more, and so forth. In all, there are 20–23 such divisions, resulting in 1–8 million terminal tubes. Each of these has at its end numerous blind sacs, called alveoli, where gas exchange occurs. There are about 300 million of these in man, each of which has a diameter of 75–300 $\mu$m. Breathing results in a flow of gas between the environment and the alveoli, while the right heart causes blood to flow through smaller and smaller tubes in the pulmonary circulation, and finally through a meshwork of fine capillaries encasing each alveolus, before returning to the left heart to be pumped through the body. At rest in a normal-sized person, breathing brings about 4 liters of environmental

TABLE 1. *Symbols in respiratory physiology*

| General variables | | Modifying symbols | |
|---|---|---|---|
| C | Compliance | A | Alveolar gas |
| C | Concontent | B | Barometric |
| D | Diffusing capacity | D | Dead space gas |
| f | Respiratory frequency | E | Expired gas |
| F | Fractional concentration (dry gas) | I | Inspired gas |
| P | Gas pressure | T | Tidal gas |
| R | Resistance | | |
| R | Respiratory exchange ratio | aw | Airway |
| Q | Volume of blood | w | Chestwall |
| $\dot{Q}$ | Volume of blood per unit time | es | Esophageal |
| V | Gas volume | pl | Intrapleural |
| $\dot{V}$ | Gas volume per unit time | L | Lung |
| | | rs | Total system |
| | | w | Transchestwall |
| | | L | Transpulmonary |
| | | rs | Transtotal system |
| | | a | Arterial blood |
| | | b | Blood (general) |
| | | c | Capillary blood |
| | | p | Pulmonary |
| | | t | Tissue |
| | | - | Mean value |
| | | · | Time derivative |

Thus, $P_{A_{O_2}}$ = Partial pressure of $O_2$ in alveolar gas
$Pa_{O_2}$ = Partial pressure of $O_2$ in arterial blood
$\dot{V}_{O_2}$ = $O_2$ consumption per unit time
$F_{E_{CO}}$ = Fraction of CO in dried, expired gas
$\dot{V}_A$ = Ventilation of the alveoli per minute or per second
$\dot{V}_A/Q$ = Ventilation/perfusion ratio

gas into the alveoli per minute (and about that much alveolar gas out into the environment), and the right heart pumps about 4–5.5 liters/min of blood through the pulmonary circulation. During severe exercise, the gas flow must be capable of increasing by 30–40-fold, and the blood flow by perhaps 5–6-fold.

These flows of gas and blood must be apportioned reasonably equitably among the 300 million alveoli. Personally, I find that numbers like million and billion, let alone the vastly larger ones which students of biology must deal with, are hard for me to comprehend. This same difficulty was expressed by a student of mine after reading this description, and we found that the concept of "1 million" became clearer to both of us when we calculated that 1 million seconds is equal to 11 days, 13 hours, and 47 minutes. A billion seconds is 31.7 years! A system designed to be able to distribute *one* fluid reasonably equitably to 300 million separate sites would be noteworthy. Our drip irrigation systems, which are now extensively employed and which must cause similar low flows of water out of each of thousands of "spigots" (some of which are elevated above the others because of nonflat terrain), are a hydraulic engineer's nightmare. The pulmonary

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distribution system, capable of distributing two fluids reasonably equitably among each of 300 million alveoli (some of which are above and some of which are below the pump), fair boggles the mind. In fact, although this distribution system works astonishingly well in health, the distortions of pulmonary architecture which occur pathologically can cause severe mismatching of ventilation and blood flow ($\dot{V}A/\dot{Q}$ mismatching). Under these conditions, arterialization of blood is impaired and severe disability can result.

The surface area at which these two fluids meet is very large (about 70 $m^2$) and the average distance between the gas and blood (thickness of the membranes separating the gas and blood) is a small fraction of a micron in healthy lungs. It should be intuitively obvious to the reader that both of these factors facilitate the diffusion of gases between blood and alveolar gas. Equally obvious is that a decrease of the surface area available for exchange, or a thickening of the membranes separating the blood and gas, can lead to inadequate gas exchange, poor arterialization of blood, and clinical disability.

Even in the normal, healthy individual, about 2% of the blood draining from the body tissues bypasses the gas exchange process of the lungs. This small flow of venous blood mixes with the blood that has been arterialized in the lung, lowering the $O_2$ content of the arterial blood slightly, and lowering its partial pressure of $O_2$ quite measurably. The two circulations involved in this normal, physiological "venous admixture" are the coronary and bronchial circulations. Some of the coronary venous blood returns to the heart, not through the coronary sinus, but directly into the cavity of the left heart through the thebesian veins; some of the bronchial venous blood returns to the left heart through the pulmonary veins. Various cardiovascular and pulmonary diseases can greatly increase the magnitude of the venous admixture [also called right-to-left (R-L) shunt] causing extreme clinical disability.

On a gross anatomical scale, the lungs and airways share the chest cavity with the heart and great vessels, and the esophagus. The lungs are encased in a thin membrane called the visceral pleura, and another similar membrane, called the parietal pleura, lines the chest cavity. Between the two membranes is a very thin film of fluid that allows the two surfaces to slide past one another easily; but normally, the membranes cannot separate from one another. Why they must stay closely apposed to one another was succinctly summarized by Jere Mead in April, 1961 when he wrote in *Physiological Reviews:*

> Regard the occupancy of the chest cavity as a competition between solids, liquids, and gases. The liquids are removed down to a vestige because the capillary pressure in the visceral pleura is considerably lower than its colloid osmotic pressure. The gases are removed because the total gas pressure in venous capillary blood is considerably less than atmospheric due to the relative capacity of blood for carbon dioxide and oxygen. The lungs, chest wall, and diaphragm are then pressed into service by atmospheric pressure and occupy the space, as it were, by default.

So, normally the lungs and chest wall must move as a unit; the lung volume only changes by a liter if the chestwall volume has also changed by a liter. I emphasize this here because the diagrams we tend to make of the respiratory system often

show the lungs as a smallish balloon inside a large chest cavity. We do this so that there is plenty of room to write in pressures and volumes, but the student should remember that anatomical accuracy is sacrificed in this effort.

## MUSCLES OF RESPIRATION

Normally, in quiet breathing, the inspiratory muscles pull the respiratory system above its "equilibrium volume" [Functional Residual Capacity (FRC)], then relax, allowing the elastic recoil of the system to effect expiration passively. The main inspiratory muscles are the diaphragm and the external intercostal muscles, and in quiet breathing, the diaphragm may be the only active inspiratory muscle. The diaphragm is attached all along the circumference of the lower thoracic cavity; its contraction pulls its central part down, enlarging the thoracic cavity. The motor nerves to the diaphragm leave the spinal cord in the ventral roots of C 3–5, and travel in the phrenic nerves. The external intercostal muscles are innervated by intercostal nerves, which leave the spinal cord in T 1–11. Their contraction raises the anterior end of each rib, pulling it upward and outward, and increasing the anterior–posterior diameter of the thoracic cavity. Other muscles, the "accessory" muscles of inspiration, become active only when breathing is greatly increased, as in severe muscular exercise. These include the scalenes, the sternocleidomastoids, the trapezii, and various muscles that reduce resistance to air flow. Maximal contraction of the inspiratory muscles with the glottis closed (the "Müller maneuver") can cause intrapleural pressure to become 60–100 mm Hg less than atmospheric.

Although expiration is passive during quiet breathing, it can become active when breathing is greatly increased or when significant airway obstruction exists. The abdominal muscles (including the rectus abdominus, external oblique, internal oblique, and transversus abdominus) are the principal expiratory muscles. They are innervated by nerves emerging from the spinal cord at the last six thoracic segments and at the first few lumbar ones. Their contraction increases intraabdominal pressure, thus forcing the diaphragm upward and increasing intrapleural and intrapulmonic pressures. They are absolutely essential for such functions as coughing, straining, and vomiting. The internal intercostals can also aid expiration and are innervated by intercostal nerves leaving the spinal cord at T 1–11. Forced maximal contraction of the expiratory muscles against a closed glottis (Valsalva's maneuver) can result in sustained intrapulmonary pressures above 100 mm Hg. Such pressures in the abdomen and chest will decrease venous return to the heart from the lower extremities and from the head and upper extremities. You already know that less cardiac input means less cardiac output; less cardiac output means less cerebral circulation; less cerebral circulation can mean loss of consciousness in seconds. This sequence of events leads to CNS asphyxia and unconsciousness even more rapidly if a period of hyperventilation (which constricts cerebral vessels) precedes the Valsalva maneuver.

## SYMBOLOGY

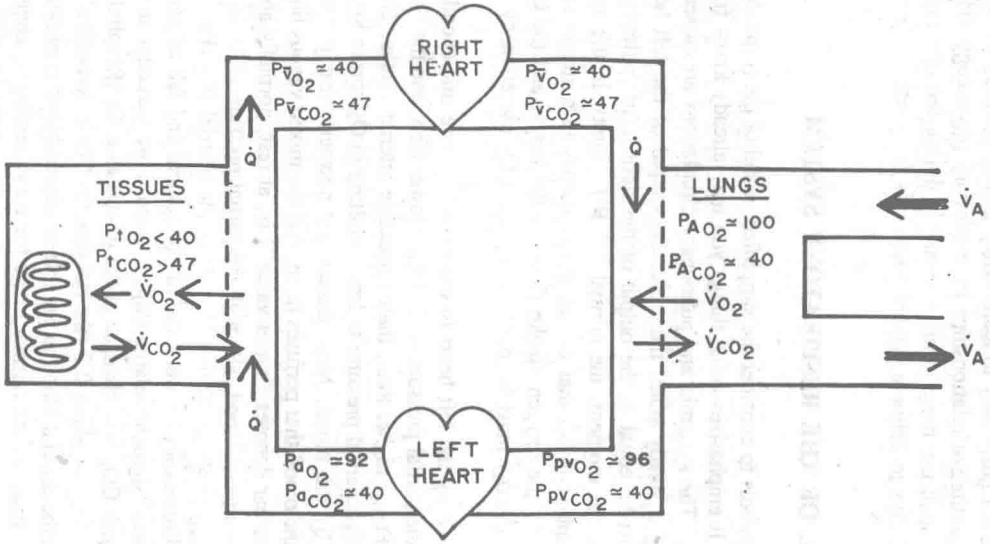
In 1951 a group of respiratory physiologists reached a consensus on a system of symbols to be used in respiratory physiology. With very few exceptions, these are used by all workers in the field today. They are internally consistent and well conceived, which makes them fairly easy to learn. They greatly simplify the consideration of the many quantitative relationships in respiratory physiology. They are listed in Table 1. We shall use these terms extensively during the respiration chapters, but I shall try always to define a symbol when it is first used.

## A MODEL OF THE RESPIRATORY SYSTEM

Let us first use these symbols to consider the simplified model of the respiratory system shown in Fig. 1. It emphasizes some things you may already know from cardiovascular physiology. The systemic and pulmonary circulations are in series with one another. During a steady state, therefore, the output of the left heart (systemic circulation) must be equal to the output of the right heart (pulmonary circulation) (ignoring, for the moment, the normal 2% R-L shunt). In the same way, the oxygen consumption ($\dot{V}O_2$) that occurs at the tissues in a steady state must be exactly matched by the oxygen uptake ($\dot{V}O_2$) in the lungs, and the $CO_2$ production at the tissues ($\dot{V}CO_2$) must be matched by the $CO_2$ excretion by the lungs ($\dot{V}CO_2$).

Arterial blood is pumped by the left heart to the tissues, where mitochondrial metabolism keeps the tissue partial pressure of $O_2$ ($Pt_{O_2}$) lower than, and the tissue partial pressure of $CO_2$ ($Pt_{CO_2}$) higher than, their respective arterial values. Thus, both gases diffuse from high partial pressure to low, resulting in $O_2$ uptake by the tissues and $CO_2$ uptake by the blood. Most tissues use nowhere near the total amount of $O_2$ present in the blood that perfuses them, and the mixed venous blood oxygen content ($C\bar{v}_{O_2}$; the bar denotes "mean value") is, at rest, normally about 75% of what it was in the arterial blood, although the partial pressure of $O_2$ in the mixed venous blood ($P\bar{v}_{O_2}$) is about 40 mm Hg, while the arterial $P_{O_2}$ ($Pa_{O_2}$) is near 100 mm Hg. This discrepancy between the fall of content and fall of partial pressure reflects the unusual sigmoid relationship between those variables in the case of $O_2$. Almost as much $CO_2$ is exchanged at the tissues as is $O_2$ [Respiratory Quotient (R.Q.) = $\dot{V}CO_2/\dot{V}O_2$ = about 0.8 (the dot denotes "time derivative")], yet the rise of $P_{CO_2}$ from the arterial blood to the mixed venous blood is normally only about 6–8 mm Hg. Thus, in the normal range the curve relating content of $CO_2$ to its partial pressure has a very different shape from that of the $O_2$ curve.

The mixed venous blood is then pumped by the right heart to the lungs where it exchanges with alveolar gas, losing $CO_2$ to the gas and gaining $O_2$ from it. The partial pressures in the mixed pulmonary venous blood are normally very nearly the same as those in mixed alveolar gas, and the partial pressures and contents in arterial blood are again very nearly the same as those in mixed pulmonary venous blood. The alveolar ventilation ($\dot{V}A$) brings a flow of fresh environmental gas,




IN STEADY STATE:

$$\dot{V}_{CO_2\,tissues} = \dot{V}_{CO_2\,lungs} = \dot{Q}[C\bar{v}_{CO_2} - Ca_{CO_2}] = \dot{V}_A[F_{ACO_2} - F_{ICO_2}]$$

$$\dot{V}_{O_2\,tissues} = \dot{V}_{O_2\,lungs} = \dot{Q}[Ca_{O_2} - C\bar{v}_{O_2}] = \dot{V}_A[F_{IO_2} - F_{AO_2}]$$

$$\dot{Q}\ right\ heart = \dot{Q}\ left\ heart$$

**FIG. 1.** A simplified model of the respiratory system. $P_{CO_2}$ and $P_{O_2}$ are given normal, resting sea-level values in the tissues ($P_{tO_2}$), in the mixed venous blood ($P\bar{v}_{O_2}$), in the alveolar gas ($P_{AO_2}$), in mixed pulmonary venous blood ($P\bar{p}v_{O_2}$), and in the arteries ($Pa_{O_2}$).

which is rich in $O_2$ (20.95%) and almost free of $CO_2$ (0.04%), through the alveoli. This flow of gas tends to replace the $O_2$ taken up by the blood and to carry the $CO_2$ given off by the blood out into the environment. Again in the steady state, the amounts of $O_2$ and $CO_2$ exchanged at the alveolar membranes must be equal to the amounts exchanged with environment per minute.

## PRESSURE PROFILE OF $O_2$ FROM ENVIRONMENT TO MITOCHONDRION

The respiratory system can also be viewed as a delivery system that passes $O_2$ down a series of steps between environment and mitochondrion, as seen in Fig. 2. There is a limited "pressure head" for that delivery, which is set by $P_{O_2}$ in the environmental gas, which in turn is determined by the barometric pressure times the fraction of the dry gas molecules which are $O_2$ ($P_B \times F_{O_2}$). If the environmental gas is totally dry, which normally occurs only if a subject breathes from a tank of dried compressed air, then the environmental $P_{O_2} = 760 \times 0.2095 = 159$ mm Hg. It is easy to see that lowering either $P_B$ (as in the ascent to high

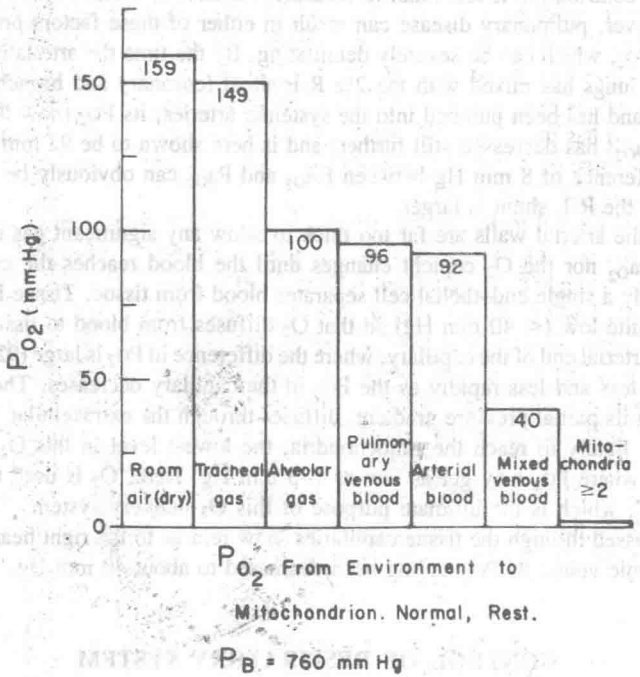



**FIG. 2.** Oxygen pressure profile from environment to mitochondrion in a normal resting male at sea level.

altitude) or $F_{O_2}$ (as in breathing a mixture of air and $N_2$) will lower the available "pressure head" for $O_2$ delivery, and tend to lower the maximum possible $\dot{V}_{O_2}$. As soon as the gas enters the warm, moist respiratory tract it is humidified, and by the time it reaches the trachea it has become saturated with water vapor. At a body temperature of 37°C, the water vapor pressure is 47 mm Hg, and the total pressure exerted by the other gases ($O_2$, $N_2$, $CO_2$, etc.) can then be only 760 − 47 = 713 mm Hg. The $P_{O_2}$ in the trachea, defined as the inspired $P_{O_2}$ ($P_{I_{O_2}}$), is then ($P_B - P_{H_2O}$) ($F_{I_{O_2}}$) = 713 mm Hg (0.2095) = 149 mm Hg. So, $P_{O_2}$ decreased as the gas became humidified, simply because the water vapor diluted the $O_2$. The gas then passes into the alveoli where its $P_{O_2}$ (the $P_{A_{O_2}}$) is determined by a balance of two processes. The alveolar ventilation ($\dot{V}_A$) brings a flow of $O_2$-rich gas into the alveoli and tends to raise $P_{A_{O_2}}$, while the pulmonary blood flow ($\dot{Q}$) removes $O_2$ from the alveolar gas and tends to lower $P_{A_{O_2}}$. As $\dot{V}_A$ increases, clearly $P_{A_{O_2}}$ will tend to be brought closer to $P_{I_{O_2}}$, and vice versa. In this case, $P_{A_{O_2}}$ is shown to be a nice, normal sea-level value of 100 mm Hg. The pulmonary venous blood, here shown to have a $P_{O_2}$ of 96 mm Hg, normally has a slightly lower $P_{O_2}$ than the mixed alveolar gas. The two possible contributors to this drop of $P_{O_2}$ are $\dot{V}_A/\dot{Q}$ mismatching and diffusion difficulties, but normally at sea level the latter contribution is too small to measure. As already mentioned in this chapter, however, pulmonary disease can result in either of these factors producing a drop in $P_{O_2}$, which can be severely debilitating. By the time the arterialized blood from the lungs has mixed with the 2% R-L shunt (coronary and bronchial circulations), and has been pumped into the systemic arteries, its $P_{O_2}$ (now the arterial $P_{O_2}$ or $P_{a_{O_2}}$) has decreased still further, and is here shown to be 92 mm Hg. This small difference of 8 mm Hg between $P_{A_{O_2}}$ and $P_{a_{O_2}}$ can obviously be increased greatly if the R-L shunt is larger.

Since the arterial walls are far too thick to allow any significant gas exchange, neither $P_{a_{O_2}}$ nor the $O_2$ content changes until the blood reaches the capillaries, where only a single endothelial cell separates blood from tissue. Tissue $P_{O_2}$ ($P_{t_{O_2}}$) is kept quite low (< 40 mm Hg) so that $O_2$ diffuses from blood to tissue rapidly near the arterial end of the capillary, where the difference in $P_{O_2}$ is large (92 − $P_{t_{O_2}}$), and then less and less rapidly as the $P_{O_2}$ in the capillary decreases. The $O_2$, still following its partial pressure gradient, diffuses through the extracellular fluid, into the cells, finally to reach the mitochondria, the lowest level in this $O_2$ transport cascade, where $P_{O_2}$ may get as low as 1–3 mm Hg. Here, $O_2$ is used to oxidize $H_2$ and C, which is the ultimate purpose of this $O_2$ delivery system. The blood, having passed through the tissue capillaries, now returns to the right heart through the systemic veins, its $P_{O_2}$ having been decreased to about 40 mm Hg.

## CONTROL OF RESPIRATORY SYSTEM

Unlike the heart, which has its own intrinsic rhythm, the respiratory muscles do not "beat" on their own, and therefore respiration needs to have neural systems capable of generating amd maintaining a regular breathing cycle to carry out

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