RESPIRATORY DISORDERS

A Pathophysiologic Approach

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SECOND EDITION

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We wish to dedicate this book to our wives,
Nancy, Dwyn, Diana, and Lois
for their patience and support.

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Preface

IT HAS BEEN MORE than seven years since the first edition of this book appeared under the title *Respiratory Insufficiency*. Since that time, there have been dramatic changes in the practice of chest medicine. To incorporate these changes, extensive revisions of the original text were required, particularly in regard to acute respiratory failure, ventilator care, and diseases affecting airways function. Since we now realize that the previous title of the book did not accurately reflect its scope and since the present text differs so greatly from the first, the previous title has been replaced by one which is similar to others in this Year Book Internal Medicine Series.

Morbidity and mortality from chronic respiratory diseases have increased notably during the past 25 years. A vast and often confusing literature on the pathophysiology, diagnosis, and treatment of these disorders has accumulated over the same period. The present volume attempts to review these subjects in simple, nonmathematical terms. It emphasizes the relationships of functional abnormalities to diagnosis, natural history, and therapy for respiratory diseases.

Following a glossary of commonly used symbols and terms, the volume is divided into three parts. The first presents a brief review of normal pulmonary physiology, emphasizing concepts that have direct clinical applications. In the second part, the pathophysiology, differential diagnosis, and management of various manifestations of bronchopulmonary dysfunction are discussed. The last part deals with categories of diseases which affect bronchopulmonary function. Since the type of dysfunction produced by a respiratory disease is generally more closely related to its anatomical location than to its specific etiology, this part is organized along anatomical lines. No attempt is made to provide a comprehensive survey of chest diseases. Specific pulmonary infections and neoplasms receive scant attention, and nonphysiologic diagnostic methods are largely ignored, despite their obvious importance in the diagnosis of pulmonary diseases. Disorders that manifest themselves primarily by the dysfunction they produce are given major emphasis. Their pathogenesis, diagnosis, physiologic consequences, and treatment are discussed.

Throughout we have directed the discussion to medical students and physicians who have had no special training in pulmonary diseases, and we have attempted to provide the basic knowledge of pathophysiology of the lung needed for diagnosis and management of most respiratory dysfunction.

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Terminology, Abbreviations, and Symbols

IN THE FIELD of respiration there is a standard terminology, and certain conventions are recognized concerning symbols and abbreviations. In the interests of readability, definitions are given as terms appear in the text. For reference, however, the following glossary is provided. The terminology is based on recommendations published in the *American Thoracic Society News*, 3:6, 1977, and 4:12–15, 1978.

General Symbols

V	volume of a gas
F	fractional concentration of a gas
P	pressure
Q	volume of blood
C	content or concentration in blood
S	saturation of blood
%X	Percent sign preceding a symbol indicates percentage of the predicted normal value
X/Y%	Percent sign *after* a symbol indicates a ratio function with the ratio expressed as a percentage. Both components of the ratio must be designated; e.g., $FEV_1/FEV\% = 100 \times FEV_1/FVC$
f	Frequency of any event in time, e.g., respiratory frequency: the number of breathing cycles per unit of time
t	Time
anat	Anatomical
max	Maximum

A dot above a symbol indicates the time derivative of the value. (Thus V indicates volume, whereas $\dot{V}$ indicates volume per unit time, or flow.) A dash above the symbol indicates the mean value. In composite abbreviations, other letters appear as suffixes, either as small capital letters or subscripted symbols. These suffixes are as follows:

I	Inspired
E	Expired
A	Alveolar
T	Tidal
D	Dead space
B	Barometric
STPD	Standard temperature and pressure, dry. These are the conditions of a volume of gas at 0° C, at 760 torr, without water vapor
BTPS	Body temperature (37° C), barometric pressure at sea level (760 torr), and saturated with water vapor
ATPD	Ambient temperature and pressure, dry

ATPS	Ambient temperature and pressure, saturated with water vapor
L	Lung
b	Blood in general
a	Arterial. Exact location to be specified in text when term is used
v	Venous. Exact location to be specified in text when term is used
$\bar{v}$	Mixed venous
c	Capillary. Exact location to be specified in text when term is used
c′	Pulmonary end-capillary

Ventilation and Respiratory Mechanics

Volumes are expressed in liters (BTPS), flow in L/sec, and pressure in cm H_2O.

TLC	Total lung capacity: volume of gas in the lungs at maximum inspiration
RV	Residual volume: volume of gas remaining in the lungs at maximum expiration
VC	Vital capacity: maximum volume excursion of which the lungs are capable by voluntary effort (TLC − RV = VC)
IVC	Inspiratory vital capacity: vital capacity measured by maximal inspiration from residual volume
FVC	Forced vital capacity: vital capacity measured by rapid forced expiration from TLC to RV
FEV_1	Forced expiratory volume in one second: volume expired in the first second of the FVC maneuver
FRC	Functional residual capacity: volume of gas in the lung at the end of a normal tidal breath when respiratory muscles are relaxed
V_T	Tidal volume: volume of gas inspired or expired with each breath
V_D	Physiologic dead space: calculated volume (BPTS), which accounts for the difference between the pressures of CO_2 in expired gas and arterial blood. Physiologic dead space reflects the combination of anatomical dead space and alveolar dead space, the volume of the latter increasing with the importance of the *nonuniformity* of the ventilation/perfusion ratio in the lung
$V_{D_{anat}}$	Volume of the anatomical dead space (BTPS)
V_{D_A}	The alveolar dead-space (BTPS): $V_{D_A} = V_D = V_{D_{anat}}$
PEF	Peak expiratory flow (L/min or L/sec)
$*\dot{V}max_{XX\%}$	Maximum expiratory flow (instantaneous) qualified by the volume at which measured, expressed as percent of the FVC that has been exhaled. (Example: $\dot{V}max_{75\%}$ is the maximum expiratory flow after 75% of the FVC has been exhaled and 25% remains to be exhaled)
$\dot{V}max_{XX\%TLC}$	Maximum expiratory flow (instantaneous) qualified by the volume at which measured, expressed as percent of the TLC that remains in the lung. (Example: $\dot{V}max_{40\%TLC}$ is the maximum expiratory flow when 40% of the TLC remains in the lung)

*There has been confusion in the literature concerning this abbreviation. At times $\dot{V}max_{25\%}$ has been used instead of $\dot{V}max_{75\%}$ to indicate flow after exhalation of the first 75% of the FVC.

FEF_{x-y} Forced expiratory flow between two designated volume points in the FVC. These points may be designated as absolute volumes starting from the full inspiratory point or by designating the percent of FVC exhaled

$FEF_{.2-1.2L}$ Forced expiratory flow between 200 ml and 1,200 ml of the FVC; formerly called maximum expiratory flow

$FEF_{25\%-75\%}$ Forced expiratory flow during the middle half of the FVC; formerly called maximum midexpiratory flow

MVV Maximum voluntary ventilation: maximum volume of air that can be breathed per min by a subject breathing quickly and as deeply as possible. The time of measurement of this tiring lung function test is usually between 12 and 30 sec, but the test result is given in L(BTPS)/min.

$\dot{V}_E$ Expired volume per min (BTPS)

$\dot{V}_I$ Inspired volume per min (BTPS)

$\dot{V}_{CO_2}$ Carbon dioxide production per min (STPD)

$\dot{V}_{O_2}$ Oxygen consumption per min (STPD)

R Respiratory exchange ratio in general. Quotient of the volume of CO_2 produced divided by the volume of O_2 consumed

$\dot{V}_A$ Alveolar ventilation: physiologic process by which alveolar gas is removed and replaced with fresh gas. The volume of alveolar gas actually expelled completely is equal to the tidal volume minus the volume of the dead space.

$\dot{V}_D$ Ventilation per min of the physiologic dead space (BTPS)

$\dot{V}_{D_{anat}}$ Ventilation per min of the anatomical dead space, that portion of the conducting airway in which no significant gas exchange occurs (BTPS)

$\dot{V}_{D_A}$ Ventilation of the alveolar dead space (BTPS), defined by the equation:

$$\dot{V}_{D_A} = \dot{V}_D - \dot{V}_{D_{anat}}$$

Paw Pressure at any point along the airways

Pao Pressure at the airway opening; i.e., mouth, nose, tracheal cannula

Ppl Pleural pressure: the pressure between the visceral and parietal pleura relative to atmospheric pressure, in cm H_2O

Palv Alveolar pressure

P_L Transpulmonary pressure: transpulmonary pressure, P_L = Palv − Ppl, measurement conditions to be defined

Pst(L) Static recoil pressure of the lung; transpulmonary pressure measured under static conditions

Pbs Pressure at the body surface

Pes Esophageal pressure used to estimate Ppl

Pw Transthoracic pressure: pressure difference between parietal pleural surface and body surface. Transthoracic in the sense used means "across the wall." Pw = Ppl − Pbs

Ptm Transmural pressure pertaining to an airway or blood vessel

Prs Transrespiratory pressure: pressure across the respiratory system. Prs = Palv − Pbs = P_L + Pw

R Flow resistance: the ratio of the flow-resistive components of pressure to simultaneous

	flow in cm H_2O/L/sec
Raw	Airway resistance calculated from pressure difference between airway opening (Pao) and alveoli (Palv) divided by the airflow, cm H_2O/L/sec
R_L	Total pulmonary resistance includes the frictional resistance of the lungs and air passages. It equals the sum of airway resistance and lung tissue resistance. It is measured by relating flow-dependent transpulmonary pressure to airflow at the mouth
Rrs	Total respiratory resistance includes the sum of airway resistance, lung tissue resistance, and chest wall resistance. It is measured by relating flow-dependent transrespiratory pressure to airflow at the mouth.
Rus	Resistance of the airways on the upstream (alveolar) side of the point in the airways where intraluminal pressure equals Ppl (equal pressure point), measured during maximum expiratory flow
Rds	Resistance of the airways on the downstream (mouth) side of the point in the airways where intraluminal pressure equals Ppl, measured during maximum expiratory flow
Gaw	Airway conductance, reciprocal of Raw
Gaw/V_L	Specific conductance expressed per liter of lung volume at which Gaw is measured
C	Compliance: the slope of a static volume-pressure curve at a point, or the linear approximation of a nearly straight portion of such a curve expressed in L/cm H_2O or ml/cm H_2O
Cdyn	Dynamic compliance: the ratio of the tidal volume to the change in intrapleural pressure between the points of zero flow at the extremes of tidal volume in L/cm H_2O or ml/cm H_2O
Cst	Static compliance, value for compliance determined on the basis of measurements made during periods of cessation of airflow
C/V_L	Specific compliance: compliance divided by the lung volume at which it is determined, usually FRC
E	Elastance: the reciprocal of compliance; expressed in cm H_2O/L or cm H_2O/ml

Gas Exchange, Transport, and Diffusion

Volumes are expressed in liters, flows in L/min, and gas pressures or tensions in torr.

$\dot{V}$	Total ventilation: The total volume of gas moved (inspired or expired) in the act of breathing during a given time interval, expressed in L/min
$\dot{Q}$	Blood flow or perfusion
DL_{CO}	Diffusing capacity of the lung for carbon monoxide
DL_{O_2}	Diffusing capacity of the lung for oxygen
PA_{O_2}	Alveolar oxygen tension (torr)
Pa_{O_2}	Arterial oxygen tension (torr)
PA_{CO_2}	Alveolar carbon dioxide tension (torr)
Pa_{CO_2}	Arterial carbon dioxide tension (torr)
Sa_{O_2}	Arterial oxygen saturation (%)

When chemical reactions are described, standard chemical symbols are used.

Respiratory Therapy Terms

GASES AND AEROSOLS

Aerosol: A suspension of fine particles of a liquid or solid in an atmosphere of gas.

Atomizer: An aerosol generator designed to produce a spray whose particle size is not maintained by baffling.

Nebulizer: An aerosol generator designed to produce particles within the therapeutic range for deposition along the airway.

Humidifier: A device used to increase water vapor content of air.

Low-Flow Oxygen System: A system in which the reservoir and total gas flow of the apparatus are insufficient to supply the entire inspired atmosphere, thus necessitating room air to comprise a portion of each tidal volume.

High-Flow Oxygen System: System in which the reservoir and total gas flow of the apparatus are sufficient to supply the entire inspired atmosphere; the ventilatory pattern should have no effect on the inspired oxygen concentration.

Nasal Cannula: A plastic appliance consisting of two tips about 1 cm in length arising from an oxygen supply tube and inserted into the anterior nares, used to deliver moderate concentrations of O_2.

Nasal Catheter (oropharyngeal catheter): A soft rubber or plastic catheter with several holes in its terminal 2 cm. The device is inserted into the oropharynx and is used to deliver moderate concentrations of oxygen.

T-piece (T tube): T-shaped tube designed to administer an aerosol and supplemental oxygen to patients with endotracheal or tracheostomy tubes.

Simple Mask: A face mask in which there is free mixing of both inspired and expired air.

Partial Rebreathing Mask: A face mask and a reservoir bag permitting a portion of the exhaled gas to enter the bag for mixing with source gas.

Nonrebreathing Mask: A face mask designed to separate flow of inspired and expired gases.

Venturi Mask: A face mask designed to entrain atmospheric air to provide a constant fractional dilution of a pressurized gas, most commonly oxygen. Within limits, the concentration of the gas delivered is independent of the gas flow.

CHEST PHYSICAL THERAPY

Postural Drainage (bronchial drainage): Positioning of a patient, usually during deep breathing and coughing, so that the drainage of secretions from various areas of the lungs is augmented by gravity.

Chest Wall Percussion: Clapping with cupped hands or with a mechanical device on the chest wall over draining areas of the lungs, usually performed with postural drainage.

Chest Wall Vibration: Manual or mechanical vibration and gentle application of pressure on the chest wall over draining areas of the lungs, usually performed with postural drainage.

MECHANICAL VENTILATION

Intermittent Positive-Pressure Breathing (IPPB): Pressure greater than atmospheric at the airway opening during inspiration, used to assist or support ventilation. During expiration, pressure returns to atmospheric.

Positive End-Expiratory Pressure (PEEP): A residual pressure greater than atmospheric maintained at the airway opening at the end of expiration.

Negative-Pressure Ventilation: A negative pressure applied to the thorax to assist or support ventilation.

Continuous Positive Airway Pressure (CPAP): A pressure greater than atmospheric, maintained at the airway opening throughout a spontaneous respiratory cycle.

Expiratory Positive Airway Pressure (EPAP): A pressure greater than atmospheric, maintained at

the airway opening only during the expiratory phase of a spontaneous respiratory cycle.

Continuous Positive Pressure Ventilation (CPPV): Pressure greater than atmospheric at the airway opening during inspiration, used to support ventilation in conjunction with a pressure greater than atmospheric maintained at the airway opening at the end of expiration; i.e., IPPB plus PEEP.

Controlled Ventilation: Manual or mechanical ventilation in which the frequency of breathing is determined by a ventilator according to a preset cycling pattern without initiation by the patient.

Assisted Ventilation: Manual or mechanical ventilation in which the patient initiates inspiration and establishes the frequency of breathing.

Assist-Control Ventilation: Manual or mechanical ventilation in which the minimum frequency of breathing is predetermined by the ventilator controls, but the patient has the option of initiating inspiration to give a faster rate.

Intermittent Mandatory Ventilation (IMV): Periodic controlled ventilation with inspiratory positive pressure, with the patient breathing spontaneously between controlled breaths.

Synchronized Intermittent Mandatory Ventilation (SIMV): Periodic assisted ventilation with inspired positive pressure, with the patient breathing spontaneously between assisted breaths.

Volume-constant Ventilator: A device for delivering a preset inspired volume irrespective, within specified limits, of the pressure required to deliver that volume.

Pressure-limited Ventilator: A device designed to deliver inspired gas until a preset level of airway pressure is reached.

Contents

PART I

Normal Physiology

1

Overview of the Respiratory System

THE HUMAN BODY may be regarded as a machine that requires energy to function. The energy is derived from the burning of fuel, a form of combustion that requires oxygen. Oxygen is obtained from the surrounding atmosphere and transported to the metabolizing cells within the body. The cells' combustion products are delivered, in turn, to the atmosphere. It is the primary function of the respiratory system to supply oxygen and to rid the body of carbon dioxide, the product of combustion. This process is complicated by the fact that man, as a whole organism, exists in a gaseous environment, breathing air, whereas the metabolizing cells function in a fluid milieu. Thus, the oxygen and carbon dioxide must be transferred between gas and liquid phases.

In order to accomplish its function, the respiratory system uses a reciprocating pump to move air into and out of the body. This pump has several interacting components. The air passes through a system of flexible, compliant branching tubes that offer resistance to air flow. The lung as a mechanical pump is a volume-elastic structure with certain physical characteristics. It is housed in a semi-rigid container, the thorax. This structure is acted upon by the respiratory muscles acting synchronously. The muscles driving the respiratory pump are under the control of the central nervous system, which, in turn, is responsive to the metabolic demands of the body. Within the lung, a large and vulnerable surface is exposed to the potentially hostile external environment. Therefore, the lung possesses mechanisms to defend itself from injury.

To transfer oxygen and carbon dioxide between gas and liquid, the two phases must be brought into intimate contact while their separation is maintained by a thin membrane. The transfer of gas across the membrane is facilitated by an extensive pulmonary capillary bed, which provides a large surface for gas exchange; an alveolar anatomy, which provides a short path length for gas diffusion; and biochemical mechanisms, which allow the rapid movement of oxygen and carbon dioxide across the membrane. For maximum efficiency of gas exchange, blood flow and ventilation should be similarly distributed throughout the lung.

In the liquid or blood phase a transport mechanism for respiratory gases must be available that has a greater capacity than that provided by physical solution alone. Hemoglobin supplies this transport mechanism. An efficient circulatory pump, the heart, provides the mechanical apparatus to transport the respiratory gases between lungs and tissues.

In the following pages of this part, various facets of the normal respiratory system will be described. This is not intended to be a complete and detailed description of respiratory physiology. Rather, it is intended to provide a background that may form the basis for understanding and dealing with derangements in function caused by disease.

2

Lung Defense Mechanisms

THE RESPIRATORY SYSTEM, moving air into and out of the lung and presenting a large surface for gas exchange, is constantly and extensively exposed to a potentially hostile environment. Yet man can live in a variety of situations varying in temperature, humidity, and degree of atmospheric contaminants. Mechanisms exist that temper the air we breathe and defend the lung against insult or injury.

The Upper Airway

Whether we reside in a frigid or tropical clime, the inspired air reaching the lower respiratory tract is adjusted to a temperature close to 37 C. The nasal passages constitute an effective air conditioning unit. The rich vascular supply of the nasal turbinates coupled with the fact that the air-stream passing them is not much wider than 1 mm makes the turbinates an effective heat exchanger. Humidification of inspired air is also accomplished primarily in the nasal passages through an outpouring of nasal secretions. It is estimated that the volume of nasal secretion amounts to a liter or more per 24-hour period. The air reaching the lower air passages, therefore, is almost fully saturated as well as close to body temperature. In susceptible individuals bypassing or overwhelming the air conditioning function of the nasal passages by exercise or breathing cold air results in clinical bronchospasm (see chap. 27).

Each liter of urban air contains vast amounts of particulate matter. Various mechanisms are available to deal with such foreign material. The nasal passages constitute the first line of defense. The hairs of the nares filter out the larger particles. Most of the remaining particles greater than 10 μ in diameter settle or impact upon the mucus coating the nasal passages. As water is added to the inspired air, hygroscopic particles increase in size, rendering them more likely to deposit in the upper respiratory tract. Almost no particles larger than 10 μ and only 15% of those greater than 4.5 μ reach the level of the larynx.

The Mucociliary Escalator

The airways are lined with ciliated columnar epithelium. This epithelium is pseudostratified in large airways but becomes single-layered and finally cuboidal with subsequent generations of branching. The surface contains approximately five ciliated cells for each mucus-secreting goblet cell. The proportion of goblet cells diminishes in peripheral airways and they are altogether absent in terminal bronchioles. Ciliated cells may be found distally as far as in the respiratory bronchioles. Mixed serous and mucus-producing cells are seen in the bronchial glands. These glands are most numerous in medium bronchi, plentiful in the trachea and large bronchi, less numerous in small bronchi, and absent in bronchioles. These cellular elements and the secretions overlying them make up the mucociliary escalator.

Inhaled particles entering the trachea are for the most part smaller than 10 μ. Most of the

particles greater than 2 μ deposit on the sticky mucus layer lining the tracheobronchial tree. Because of their inertia, particles tend not to follow flow stream lines at points of branching. As a result, particle deposition is greater at airway bifurcations. Only particles smaller than 2 μ are likely to reach the level of the alveoli.

It has been estimated that from 10 to 100 ml of tracheobronchial mucus is produced daily in the normal adult. This mucus blanket protects the underlying mucosa from dehydration as well as functions as an important cleansing mechanism. The mucus blanket is about 5 μ thick and appears to consist of a thin, watery solution covered by a more tenacious viscoelastic gel layer. The adhesive character of the gel layer enables it to trap and hold the particles that impinge upon it. The thinner solution layer has a high rate of shear, and it is within this layer that the cilia beat to move the mucus carpet upward toward the glottis.

Each ciliated cell bears about 200 cilia 5–7 μ long. The cilia beat in a synchronized fashion at a rate of between 1,000 and 1,500 times a minute. When the forward effective stroke achieves its maximum velocity, the tips of the cilia come in contact with the gel layer, moving it along. The recovery stroke is slower, taking three times as long as the forward stroke, and occurs in the solution layer. By this mechanism the mucus carpet is propelled upward at between 1 and 3 cm/min. Ultimately, the mucus bearing the captured particulates reaches the level of the pharynx, where it is swallowed. If the quantity is sufficient to stimulate the upper tracheobronchial tree, cough and expectoration may assist the removal of mucus.

This important and normally effective clearance mechanism may be altered by bacteriologic or chemical insults. Tobacco smoke and certain air pollutants have deleterious effects. Increase in mucus secretion or alteration of the character of mucus in response to such insults can diminish the effectiveness of this mechanism. Decrease in ciliary activity and damage to or even loss of ciliated cells further interferes with transport. Goblet cell hyperplasia or increase in number of bronchial glands contributes further secretions to the transport burden. Although increased stimulus to cough may assist in removal of these excessive secretions, mucus plugging may occur at a more peripheral level when the transport mechanism is overwhelmed.

Cough

Cough may result from mechanical irritation or chemical stimulation of the tracheobronchial tree. Cough due to chemical irritants occurs when the irritant is drawn deep into the lungs but exhibits ready tachyphylaxis on continued exposure. Mechanical irritation, however, continues to stimulate cough even on repetition. The larynx, tracheal bifurcation, and points of lobar branching are most sensitive to mechanical irritation. The sensory end-organs located here and in the posterior wall of the trachea transmit afferent impulses via the vagus to the medulla.

The cough sequence is a familiar one. Rapid inspiration is followed by generation of an expiratory effort against the closed glottis. At the peak of this effort, rapid opening of the glottis is followed by vigorous, almost explosive expiration. Frequently, a series of coughs may follow the initial inspiration, each one occurring at a progressively lower lung volume.

The intrathoracic or pleural pressure generated by the expiratory muscles during cough may be high, often in excess of 200 cm H_2O. When expiratory flow is permitted upon opening the glottis, the flow-limiting mechanisms described in chapter 6 come into play with establishment of equal pressure points, dynamic compression of large intrathoracic airways, and achievement of $\dot{V}max$. That discussion of the dynamic properties of the respiratory system is concerned with airflow. Since the purpose of cough is to rid the tracheobronchial tree of excess secretions, we must now consider (1) the dynamics of liquid flow in relation to airflow as the two phases move in the same direction, and (2) the manner in which these liquid secretions are mobilized in this two-phase system.

If we consider the respiratory airways as analogous to a vertical pipe conducting upward flow in both liquid and gas phases, the patterns we