CURRENT PULMONOLOGY

Volume 5

Edited by

Daniel H. Simmons, M.D., Ph.D.

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Preface

I am pleased to have compiled Volume 5 of *Current Pulmonology,* in which experts review new studies in their fields. The subject matter of the chapters has been selected to provide both basic and clinical information particularly relevant to the modern practice of pulmonology.

Bloom and Burrows discuss diseases associated with airflow limitation. They point out that the major types of obstructive disease—emphysema, bronchitis, and asthma—are really syndromes respectively related to three important host susceptibility factors: lack of protease inhibitors, bronchial reactivity to nonspecific stimuli, and a genetic tendency to form IgE (atopy). These host factors are considered separately from provocative substances in air pollution, cigarette smoke, infections, and occupational exposures. With these two sets of factors in mind, the natural histories of the three types of diseases are discussed as an important aid in diagnosing and managing disease. In particular, it is pointed out that early detection of incipient severe obstructive disease may be critical.

Bone and Balk provide a perspective on the use of mechanical ventilation, invoking the past and anticipating the future. They point out what is and is not known about the flood of new modalities, including intermittent mandatory ventilation, synchronized intermittent mandatory ventilation, assisted/controlled ventilation, inspiratory pause, end-expiratory airway pressure, and monitors of inspired oxygen concentration. Clearly, many new modalities are often being used empirically without adequate investigation of their efficacy and associated complications. The intent of all is to maintain adequate alveolar ventilation, to correct arterial hypoxemia, or to maximize oxygen transport. The last, a major determinant of tissue oxygenation, can be affected in complex ways, either positively or adversely, by both circulatory and ventilation effects of mechanical ventilation. The management of inspired oxygen concentration is being studied intensively because of its relation to oxygen toxicity. This obviously

complex system requires more knowledge of the effects of oxygen and of the need for monitoring as well as of the effects on the lung. Metabolic changes that occur during mechanical ventilation are a new and obviously important area of study. The questionable value of weaning parameters is discussed. Finally, the authors discuss high frequency ventilation, an investigative modality that may have great potential for clinical application.

The chronic interstitital lung diseases are again exhaustively discussed by Davis and Crystal, who provide an analytical update of diseases of known etiology, diseases of unknown etiology, and diseases caused by disorders of other organs. They point out recent major developments in five areas. First is the concept of alveolitis initiating chronic interstitial disease. Second is the use of bronchoalveolar lavage for determining the type of alveolitis. Third is the use of gallium-67 scanning for characterizing the type and intensity of alveolitis. Fourth is a new understanding of the mechanisms of development of interstitial fibrosis. And fifth is staging and therapy of the diseases of unknown etiology, those most studied in recent years. That the authors now list over 120 interstitial diseases of known etiology and over 40 of unknown etiology testifies to the explosive increase in information about this field. Extensive discussions of the many major diseases of known etiology emphasize that the smaller number of diseases of unknown etiology, generally used as a model for studying all interstitial disease, are not the only major problems with which we must deal. This survey is important for clinicians. It includes a very large and useful bibliography remarkable for its currency.

Fish and Menkes discuss the role of airway reactivity in both acute and chronic diseases. This is a very important aspect of obstructive disease because it may be the most treatable. Fish and Menkes make the important observation that "hyperreactivity" is a spectrum rather than an all-or-nothing phenomenon. Benefits of quantitating reactivity are discussed, and the mechanisms of reactivity—including the role of receptors, reflexes, and smooth muscle function—are examined in detail. The authors emphasize recent studies on the role of smooth muscle function, which may give clues to one very important determinant of reactivity. The relation of atopy and occupational factors to hyperreactivity is reviewed. The point is then made that hyperreactivity is clearly not synonymous with asthma but plays a role in many diseases. While hyperreactivity influences the management of chronic disease, it is not yet completely clear whether it is a risk factor for the development of chronic disease, a very important point now being studied.

Current information on the use of the fiberoptic bronchoscope is presented by Kvale. He discusses instruments now available, new techniques and their use in different clinical situations, new technologies for assisting in diagnosis, and the use of the bronchoscope in specific clinical situations.

Mountain covers management of patients with known or suspected lung

cancer. While most people would expect screening for cancer to identify a significant number of cases earlier, and earlier therapy to affect mortality, paradoxically, no effect has yet been demonstrated. (There also remains the mystery of why the incidence of various types of lung cancer seems to be changing.) The problem of early diagnosis is discussed extensively. While many "markers" for early detection have been studied, few if any have been found sensitive or specific enough to be useful. Even the chest film has a high false-negative rate—approximately 30%—at the time of the first radiologic appearance of tumor, even in the hands of well-trained radiologists. This could be a warning to clinicians! When cancer is suspected, cytology and CT scanning appear to be useful methods for preoperative diagnosis and staging, but the fiberoptic bronchoscope is still the mainstay of preoperative diagnosis. Therapy for lung cancer, whether surgery, adjuvant therapy, immunotherapy, or radiotherapy, remains discouraging. It seems likely that the best approach to reducing mortality is prevention, while the next best is "early" diagnosis.

The pathogenesis of the adult respiratory distress syndrome is reviewed by Niedermeyer, Sheller, and Brigham. In spite of considerable new information on the mechanism of development of the syndrome, clinicians are still faced with the discouraging survival rate of about 50%. One problem is that human studies of the disorder are extremely difficult. What we know is largely from carefully controlled studies on sheep and other animals, making measurements impossible on humans. It is now clear that a major factor is increased pulmonary capillary permeability, but we still do not know why or how this occurs. Nor do we know much more about therapy; for example, we still do not know whether steroids actually help. It now seems fairly clear that granulocytes sequestered in the lung from many causes result in increased permeability and pulmonary edema, and in turn cause abnormal gas exchange and lung mechanics. These observations can be related only theoretically to some of the important clinical questions, but they point to directions for human studies in the future.

Once again Sbarbaro details the surprisingly large number of recent developments in diagnosis and treatment of turberculosis. This new information is scientifically interesting and very useful to the practitioner. The section on treatment is especially important, since it includes an original summary of results of short course therapy regimens: at least four drugs are necessary for the initial phase; the continuation phase may require only two drugs; and daily drugs may not be necessary. Sbarbaro makes it clear that four-month regimens cannot be expected to be satisfactory. He concludes that short course chemotherapy is here to stay. The problem of patient compliance is now extended to the problem of physician compliance.

The burgeoning study of respiratory muscles is reviewed by Sharp. Long-known information about striated muscle can be applied almost directly to respiratory muscles, and there are already numerous applica-

tions of this information to clinical situations. The diaphragm receives special attention, since its conformation is so unique and since it is used more continuously than any other muscle in the body, and is therefore most subject to fatigue. In addition it is the main muscle of inspiration, during which most ventilatory work is done. Respiratory muscle fatigue, especially diaphragm fatigue, is clearly important to the problem of respiratory failure for CO_2. For example, it may explain the relation between increased work of breathing and hypercapnea. Clinical use of the electromyogram for monitoring respiratory muscles is discussed.

New information on fungal infection is offered by Utz. There have been a great many new developments in a field that is becoming more clinically important because of increased frequency and severity of fungal diseases in immunocompromised patients. Utz makes several important observations. For one, the incidence of disease in any region appears to be proportional to the number of myocologists available, suggesting that the apparent increase in frequency may actually be due to increasing expertise. Therapy for many nonfungal diseases is now much more sophisticated and therefore often predisposes to late fungal infections. Improved antibacterial agents often lead to terminal infections due to fungi, which are more resistant to therapy than are bacteria. Many new antifungal agents have been studied and new diagnostic techniques are being evaluated, although many of these are clearly not sensitive or specific enough for general use. Utz's review makes it clear that much of our information on fungal infections is based on case reports and studies of small series of patients. We are left with the conclusions that culture remains the gold standard for diagnosis and that amphotericin-B is still the backbone of therapy.

Nontuberculous bacterial infections are reviewed by Van Scoy. Contemporary antibiotics and their uses are discussed, with an emphasis on aminoglycosides, broad-spectrum penicillins, and cephalosporins, now standard antibacterial therapy. Prophylaxis and new groups of treatable diseases are discussed as well. The use of antibiotics has become very complicated and potentially very expensive; probably half of adult hospital antibiotic treatments are either unnecessary or inappropriate. Therefore, the section on basic principles of the use of antibiotics is a useful reminder to clinicians. Van Scoy points out common situations in which the available data on antibiotics are inadequate and where further studies should be done before the drugs can be used knowledgeably. Sophisticated use of antibiotics requires knowledge of antibacterial spectra, their pharmacologic effects and their propensity for superinfection (frequently ignored). Often, we need the help of infectious disease specialists, particularly when using recently developed cephalosporins and cephalosporinlike agents.

I would like to thank Rita Bachtold and Esther Vanegas for their help with the typing, letters, telephone calls, and so on, necessary to put this volume together. Their dedication is deeply appreciated.

Daniel H. Simmons

Contents

CHAPTER 1

Respiratory Muscles

John T. Sharp

Two body systems—the cardiovascular and the respiratory—depend upon nearly continuous rhythmic contraction of muscle throughout a person's life: The heart and the respiratory muscles both function as pumps, and although there are major differences between them, both must function continuously and nearly perfectly for a lifetime. Essential to understanding the behavior of these systems is understanding the function of the responsible muscles—the myocardium and respiratory muscles.

Since the work of Frank (1) and of Starling (2) around the turn of the century, it has been accepted that the myocardium may fail when one or both of two circumstances occurs: (1) the pressure or volume load on the heart is inordinately great and (2) the intrinsic contractile properties of the myocardium are impaired. More recently it has been recognized that the respiratory muscles also may fail and for the same reasons: (1) the mechanical load that the respiratory muscles must overcome is excessive and (2) the effectiveness of respiratory muscle contraction has been interfered with at some level. The recent recognition that respiratory failure is common, that it is a frequent cause of death, and that it can often be prevented or effectively treated has stimulated study of respiratory muscle function at both basic science and clinical levels.

To understand the function of the respiratory muscles it is necessary to have some knowledge of skeletal muscle function. Therefore, we shall begin with a review of the more important features of skeletal muscle function. Beforehand, however, we would mention three differences between the respiratory muscles and other skeletal muscles such as those of the limbs. First, the respiratory muscles must overcome principally resistive and elastic loads rather than inertial loads, as do most other muscles (3). Second, the respiratory muscles are under both voluntary and

involuntary control, and separate neural pathways exist to implement each mode of control. Third, the respiratory muscles must contract every few seconds during a lifetime and cannot rest for protracted periods as can limb muscles. Because of this third point the diaphragm, the principal inspiratory muscle, in particular has metabolic characteristics that in some respects resemble those of myocardium more than other skeletal muscles (4–9).

BASIC CONCEPTS OF SKELETAL MUSCLE PHYSIOLOGY

Mammalian Skeletal Muscle Fiber Types

In considering the properties of mammalian skeletal muscle it is of prime importance to recall that there are different kinds of skeletal muscle in any given species. Most mammalian muscles are made up of mixtures of different fiber types, which may be distinguished from one another by their histochemical and morphologic properties and by their speed of contraction (10–22). The three major muscle fiber types are (*1*) fast-twitch red (type IIA), (*2*) fast-twitch white (type IIB), and (*3*) slow-twitch intermediate (type I) (10,17,21). Some of their characteristics are summarized in Table 1.

Fast-twitch red fibers, as the designation implies, contract quickly and have short isometric contraction times and relatively high velocities of shortening. They have a high level of myosin adenosine triphosphatase (ATPase) and a reasonably well-developed glycolytic system allowing considerable anaerobic metabolism. In contrast to fast-twitch white fibers (see below) there are many mitochondria, the oxidative enzyme systems are well developed, and the fibers are relatively resistant to fatigue. The fast-twitch white fibers are similar to the fast-twitch red fibers in speed of contraction and level of myosin ATPase activity, and the glycolytic system is well developed. However, the mitochondrial oxidative system is poorly developed, and there is correspondingly poor resistance to fatigue.

Slow-twitch intermediate fibers have longer isometric twitch contraction times, lower velocities of contraction, and relatively low levels of myosin ATPase activity. Mitochondria are numerous, oxidative enzymes are well developed, and resistance to fatigue is higher than in either of the other two fiber types.

The red color of muscle is principally a result of myoglobin, which is present in fast-twitch red and slow-twitch intermediate fibers but which is nearly absent in fast-twitch white fibers.

The properties of each fiber type determine its functional deployment. Fast-twitch white fibers are used for fast, powerful, but short-term activity in which endurance and resistance to fatigue are not required. Fast-twitch red fibers are used for sustained phasic activity in which resistance to fatigue is needed. Slow-twitch intermediate fibers are economical contrac-

Table 1. Properties of the Three Muscle Fiber Types

Property or Attribute	*Fast-Twitch White*	*Slow-Twitch Intermediate*	*Fast-Twitch Red*
Fiber size (diameter)	Large	Intermediate	Small
Mitochondrial content	Low	Intermediate	High
Neuromuscular junction	Large and complex	Intermediate	Small and simple
Shortening velocity	Fast	Slow	Generally fast
Isometric twitch time	Short	Longer	Short
Oxidation enzyme activity	Low	High or intermediate	High or intermediate
Mitochondrial ATPase	Low	Intermediate	High
Glycolytic activity	High	Variable but usually low	Intermediate
Myoglobin content	Low	High	High
Glycogen content	Intermediate	Low	High
Myofibrillar ATPase (pH 9.4)	High	Low	High
Resistance to fatigue	Low	High	High
Posttetanic potentiation (PTP)	Present	Absent	Present
Twitch : tetanic tension ratio	Low	Somewhat higher	Low

tile units most suitable for slow sustained tonic contractions in which endurance and resistance to fatigue are of prime importance. An example is maintenance of posture.

It is important to realize that the size of an animal is an important determinant of the properties of its muscles (23,24). Movement in small animals is generally quicker than movement in large animals, and properties of analogous muscles reflect this difference (22,25–27). If, for example, we compare analogous muscles of the mouse and the cat, the mouse muscle will have shorter isometric twitch times, greater speeds of sarcomere shortening, and greater activity of myosin ATPase. A slow muscle in the mouse may contract faster than a fast muscle in the cat.

The diaphragm, the principal respiratory muscle, has been shown in several species to be intermediate between typical fast and slow muscles of that species (28,29). Its fiber-type composition is variable among the mammalian species; no simple scheme appears to explain the differences (15,28,30). Fiber composition of diaphragms from a number of common mammalian species is given in Table 2.

Before leaving the subject of muscle fiber types, two final points should be mentioned. The first is that neural influences determine muscle fiber type (22). If a motor nerve that normally innervates a slow muscle is transplanted into a fast muscle, the muscle will change from fast to slow. The reverse occurs when a nerve normally innervating a fast muscle is

Table 2. Characteristics of Diaphragm Muscle Fibers in 10 Mammalian Species

	Average Body Weight, Kg	*Average Respiratory Rate, Breaths/min*	*Percentage of Fiber Types*			*Average Diaphragmatic Fiber Diameter, μm*	*Mean Fiber Cross-Sectional Area, μm²*
			Fast-Twitch Red	*Fast-Twitch White*	*Intermediate Slow-Twitch*		
Mouse	0.03	110	93	None	7	18	1,110 ± 160[a]
Rat	0.3	100	34	27	39	34	1,990 ± 460
Rabbit	3	40	21	36	43	36	3,170 ± 180
Cat	4	30	16	45	39	30	3,590 ± 1720
Dog	13	20	64	None	36	—	1,690 ± 150
Sheep	45	20	43	14	43	—	1,870 ± 300
Man	70	16	21	24	55	34	—
Pig	100	—	20	35	45	60	5,680 ± 1170
Ox	500	30	24	None	76	44	3,790 ± 460
Horse	500	12	21	None	79	—	2,420 ± 560

SOURCE: Gauthier GF et al: *J Cell Biol* 28:333–354, 1966; Davies AL et al: *J Anat* 112:41–60, 1972.

[a] Mean ± standard deviation.

transplanted into a slow one. The transplanted nerve need not make functional synaptic connections with the new host muscle to effect this transformation.

The second point is that training, particularly endurance training, alters fiber composition and muscle characteristics (22). As an example, treadmill running increases the percentage of fast-twitch red fibers in the lower extremities and increases the mitochondrial content and oxidative enzyme activity of these muscles.

Mechanics of Muscle

The Fundamental Model and Its Components

The most generally accepted model of skeletal muscle, and one that describes reasonably well the behavior of both amphibian and mammalian skeletal muscle, is that of A.V. Hill (31–33). This model considers that muscle is made up of three interacting components, a contractile component, a lightly damped* series elastic component, and a parallel elastic component. The mechanical properties of contracting muscle are believed to be defined by three unique mechanical attributes of the first two of these components, namely, the force–length (length–tension) and force–velocity relationships of the contractile element and the load–extension relationship of the series elastic component. The parallel elastic element is principally responsible for the passive mechanical characteristics of relaxed muscle and plays little part in determining its active contractile properties.

Contractile Element: Its Force–Length or Length–Tension Relationship. Inactive or relaxed muscle exerts no tension when extended to lengths less than its normal resting length in the body. When stretched passively to lengths greater than its resting length it exerts tension that increases exponentially as a function of increasing length. This passive tension, believed to be exerted by the parallel elastic element, plotted against muscle length gives the passive length–tension curve. The force–length, or length–tension, curve for the contractile element of active muscle is obtained by subtracting the initial passive tension from the total tension (active plus passive force) exerted by the muscle during isometric contractions over a range of muscle lengths. This difference, active tension, is plotted against length, usually expressed as percentage of the resting in situ length, to yield the active length–tension curve. There is an optimal initial muscle length, designated L_0, at which the active tension generated is maximal. This is usually

* Lightly damped indicates that the series elastic element behaves as though there were a small resistance coupled in parallel to it, reducing somewhat the velocity with which it would recoil if suddenly released.

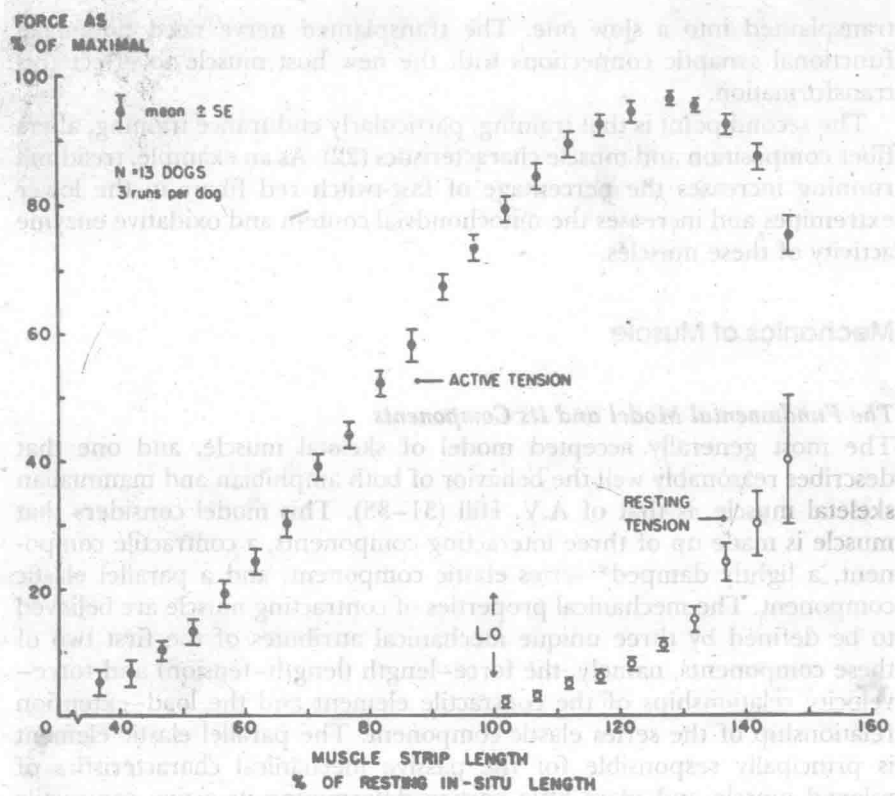

Figure 1. Active and passive length–tension diagrams obtained from a canine diaphragmatic strip preparation with intact nerve and blood supply. On the abscissa, 100% indicates the resting in situ length as determined by the first appearance of passive tension. Ordinate is force expressed as percentage of maximal active force. N = 13 dogs, three runs per dog. (From Kim et al: *J Appl Physiol* 41:369–382, 1976, by permission of authors and publisher.)

between 100 and 120% of the normal resting length in the body (resting in situ length). Figure 1 gives an example of active and passive isometric length–tension curves for a strip of dog diaphragm with intact nerve and blood supply. In most skeletal muscles, effective active tension is not generated below lengths of 40—65% of L_o. It is clear that shortening a muscle fiber below its L_0 reduces its efficiency as a force-generating mechanism.

In a classic paper, Gordon et al. (34) correlated isometric length–tension parameters of frog muscle fibers with sarcomere lengths and the extent of overlap between thick myosin filaments and thin actin filaments, assuming the sliding filament theory of contraction (Figs. 2 and 3). Isometric tension increased as a function of length in two stages. At a sarcomere length of 1.27 μm, tension was zero since there was maximal